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COMMUNICATIONS

SUB-CONJUNCTIVAL PENICILLIN AND INTRA-OCULAR INFECTION*

BY

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THE success of local penicillin in the treatment of certain superficial lesions of the eye has stimulated interest in the possible value of this remedy for deep intra-ocular infection especially since Schu-mine warfare has provided many favourable opportunities for study.

Before it can be stated that any given drug will control infection, two conditions must be fulfilled: (*a*) the organisms of the infection must be susceptible to the drug, and (*b*) the drug can be brought to bear on the organisms in effective concentration.

The first condition is difficult to determine so far as penetrating eye wounds of warfare are concerned, but the work of Bentley and Scott Thomson[1] on the bacteriology of somatic war wounds offers a clue as to what bacterial flora may generally be expected within the eye. These observers found that in Italy the S. pyogenes aureus was by far the most common pyogenic coccus present and that the Strept. pyogen. (haemolyticus) occurred in about 6 per cent. of all wounds. In a series of 100 cases examined before operation at C.C.S. level, 51 cases had pyogenic cocci in the

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wound (Hutchison). It is at this level that definitive ophthalmic surgery commences in modern warfare. The various strains of S. pyogenes aureus found were examined for penicillin resistance. It was found that whilst 20 per cent. were resistant to 0·1 unit per c.c. (parenteral therapy concentration) few organisms were able to grow in broth containing 50 units per c.c. indicating the possible beneficial results which could be expected by using the higher concentrations of local penicillin applications.

The author has reported previously[2] the results of the bacteriological examinations of the aqueous and vitreous in cases of penetrating wounds of the eye, but as these cases were all late and examined some time after the initial injury, when the inflammation was subsiding, they cannot be accepted as valid evidence of the causal organism.

The second condition of effective concentration of a drug in the eye largely depends on the routes by which the drug is administered. All possible routes for penicillin administration have been widely explored by American workers who used rabbits as their experimental animals, and a summary of their recent work follows.

Penicillin may be caused to reach the interior of the eye by the following methods:—

(1) Local applications such as instillations, ointments, iontophoresis or constant corneal baths.
(2) Subconjunctival injections.
(3) Intra-aqueous injections.
(4) Intra-vitreous injections.
(5) Intra-venous injections.
(6) Intramuscular injections.

The bacteriostatic standard adopted in this paper is that of Rammelkampf and Keefer[3] and Salter[4] namely that the maximum bacteriostatic effect against Staph. aureus is obtained by 0·1 unit penicillin concentration and against Strep. haem. by 0·01 unit penicillin concentration per c.c. serum.

(1) *Local applications.*—The penetration of local penicillin into the aqueous has been studied by Leopold and Lamotte[5] who state that it does not appear in the anterior chamber of a normal rabbit eye after single or constant instillations of drops (500 O.U. per c.c. isotonic saline) or after the application of ointment (500 O.U. per gramme Carbowax). If however, one third of the corneal epithelium is damaged or if experimental infection of the cornea (P. leptiseptica) is present then bacteriostatic quantities of penicillin will be found in the aqueous.

These observations confirmed the work of von Sallmann and Meyer[6] who also showed that the addition of wetting agents of the aerosol group was without effect on penetration.

Turning to the penetration produced by constant corneal baths

and iontophoresis von Sallmann and Meyer[6] pointed out that penicillin appeared in moderate quantity in the aqueous after a single corneal bath but that after ionisation the concentration was increased by ten times. Von Sallmann[7] also compared the amount of penicillin to be found in the aqueous after iontophoresis (2 milliamp. for 5 minutes) with that of sodium sulphacetamide after similar treatment and the amounts were about equal. When, however, experimental infection of the anterior chamber was present (S. aureus) nine of twelve eyes were saved by penicillin iontophoresis whereas only one eye was saved by sodium sulphadiazine iontophoresis.

Dunnington and von Sallmann[8] later published the results of their work on penicillin iontophoresis and experimental infection (S. aureus) of the rabbit lens. After penicillin iontophoresis of these cases infection and shrinkage of the eye was the eventual result but when direct penicillin injections were given into the lens within six hours of inoculation the eyes were saved. Their work showed that penicillin introduced into the eye by iontophoresis does not enter the lens in bacteriostatic concentration and it is likely that this route is more valuable for anterior eye infections.

Bellows[9] investigated the penetration of penicillin into the eye when constant corneal baths (20,000 O.U. per c.c.) and various ointment bases (25,000 O.U. per gramme) were used.

After the ointment was placed over the conjunctiva and cornea of a rabbit for one hour the aqueous was subjected to penicillin assay and it was found that the use of the " vanishing " type stearate base produced most penetration. However, as Bellows points out, a diffuse corneal stain followed the use of this base and probably accounted for the increased penetration.

Leopold and Lamotte[5] are also inclined to think that corneal damage accounts for the high aqueous concentrations obtained by corneal baths and iontophoresis technique. Von Sallmann[10] had previously pointed out that corneal baths of 0·5 to 1 per cent. sod. penicillin solution did cause damage to corneal epithelium and superficial stroma but that 0·1 per cent. sod. penicillin solution produced no corneal damage even by iontophoresis[11].

(2) *Subconjunctival injections.*—Bellows[9] has compared the aqueous concentration of penicillin after corneal baths with that obtained from subconjunctival injections and he found it to be much less after the injections but still to be of bacteriostatic amount.

Leopold[12] found that penicillin was detectable in the vitreous forty-five minutes after subconjunctival injections of 2,500 O.U. sod. penicillin every 3 hours for 72 hours, but that where experimental inflammation of the anterior eye was present the penicillin vitreous concentration appeared earlier and was higher.

Without previous inflammation the vitreous concentration after

45 minutes was 0·078 O.U. per c.c. whereas when the anterior chamber was infected the concentration was 0·12 O.U. per c.c. after 15 minutes and 0·51 O.U. per c.c. after 45 minutes.

(3) *Intra-aqueous injections.*—Dunnington and von Sallmann[8] have pointed out that the injection of sodium penicillin into the anterior chamber of the rabbit eye produces only a transient inflammatory reaction of mild degree.

Leopold[12] found that after an injection of 250 O.U. per c.c. into the anterior chamber, penicillin was detected in the vitreous of normal eyes at bacteriostatic concentration fifteen minutes later but that here again the vitreous concentration was much increased if previous inflammation of the anterior chamber was present. In eyes subjected to previous iridectomy the vitreous concentration rose higher than it did in normal eyes suggesting the value of the presence of penicillin in the anterior chamber in inflamed aphakic eyes.

(4) *Intra-vitreous injections.*—Von Sallmann, Meyer and di Grandi[13] found that when penicillin was injected directly into the vitreous of rabbits it remained in uneven distribution and that the concentration fell sharply for twelve hours and thereafter remained after twenty-four hours at bacteriostatic levels. In only one case did the aqueous show any bacterial inhibition after an intra-vitreous injection. These authors stress the importance of the delayed resorption of penicillin from the vitreous as a therapeutic measure. The author[2] has described one case in which penicillin was found in the vitreous of a human eye three days after an intra-vitreal injection of 2,000 O.U. sod. penicillin.

Dunnington and von Sallmann[8] have shown that one intra-vitreous injection of penicillin will constantly control susceptible vitreous infection provided the injection is given within twelve hours of inoculation.

After twenty-four hours the penicillin injection did not stop the inflammation but there was some improvement noticeable. Larger inoculations did not affect the results of treatment nor were multiple injections more beneficial than a single injection.

Von Sallmann, Meyer and di Grandi studied the effects of these injections on the eye structure and took the protein concentration of the aqueous as a measure of the irritation produced. The protein content of the normal rabbit aqueous is from 19 to 51 mg. per 100 c.c.; after one intra-vitreous injection of 0·2 normal saline (control) it rose to an average of 183·2 mg. per 100 c.c. and after 2·5 per cent. sodium penicillin it was 247 mg. per c.c. These levels were much lower than that produced by an intra-vitreous injection of 10 per cent. sodium sulphacetamide.

After one intra-vitreous injection of purified penicillin there was moderate flare and a fine veil in the vitreous which was resorbed in a short period. On section four eyes showed circumscribed retinal atrophy of 1—2 disc diameters.

A crude penicillin injection produced an accentuation of these changes with more extensive retinal damage.

When, however, a second injection was made within twenty-four hours the damage was severe, amounting to lens changes, to heavy vitreous exudates and retinal detachment.

The importance of purity in relation to toxic effects has also been stressed by Florey and Jennings[14] and later by Herrell and Nichols[15]. Von Sallmann, Meyer and di Grandi conclude therefore that a single intra-vitreal injection of purified potent penicillin is a reasonable safe procedure and is justified in the treatment of exogenous infections of the vitreous along with other adjuvant methods.

Leopold[12] using intra-vitreous injections of various concentration from 2,500 O.U. to 5 O.U. in infected eyes showed that six eyes treated with 2,500 O.U. penicillin were quiet after four weeks and that all eyes receiving more than 1,000 O.U. per injection were favourably influenced. Even in those which received amounts as low as 5 O.U. per injection the inflammation was never as severe as it was in the control eyes.

(5) *Intra-venous injection.*—The distribution of penicillin in the eye after intravenous injection has been shown by Struble and Bellows[16] to be present in decreasing quantities in the extra ocular muscles, sclera, conjunctiva, aqueous, vitreous and cornea.

Leopold[12] using intra-venous injections of 4,000 O.U. sodium penicillin per kilogram of rabbit body weight was unable to detect the drug in the vitreous of normal eyes after 180 minutes and only a trace in the vitreous of those where there was previous infection of the anterior chamber. This is not surprising in view of the experiments of Abraham and others[17] who have demonstrated the rapid excretion in high concentration in the urine of cats after intra-venous penicillin injection.

Leopold[12] investigated 12 eyes with artificial vitreous inflammation (S. aureus) and found that all the eyes were lost in spite of two hourly intra-venous injections of sod. penicillin (4,000 O.U. per kilogram of body weight) for seventy-two hours.

(6) *Intra-muscular injections.*—Similarly Leopold[12] studied the effect of intra-muscular injections of 4,000 O.U. sod. penicillin per kg. of rabbit body weight, but even with the addition of vasoconstrictors no more than a trace of penicillin reached the vitreous.

Leopold and Lamotte[5] using intra-muscular injections of 1,500 O.U. sod. penicillin per kilogram of body weight were unable to detect penicillin in the aqueous of normal eyes later, and only small quantities in those with inflammation of the anterior chamber in amounts from 0·4 unit per c.c. after fifteen minutes to 0·15 unit per c.c. after 105 minutes (average of four eyes).

Elsewhere[2] the author has reported parallel cases in man—both with regard to the presence of penicillin in the aqueous and vitreous

after intra-muscular injections and also the inability of penicillin to control intra-ocular infection when given by this route.

Seven normal eyes were removed from battle casualties as soon as possible after death. Five of these casualties had previously received a massive dose of intra-muscular penicillin on an average nine hours before. Two eyes were used as controls but the aqueous and vitreous from each of the seven eyes showed no bacterial inhibition.

In order to reduce the time interval between injection and assay, eight casualties, who were due to have a hopeless eye removed, were given massive doses of intra-muscular penicillin before operation. The enucleated eye was then subjected to assay within half an hour of removal, but again no inhibition was detectable in any of the examples.

A survey of this experimental evidence allows certain conclusions to be reached so far as rabbits are concerned, namely :—

(1) Direct intra-vitreous injections of penicillin are the most effective means of obtaining high concentrations and bacteriostasis in the vitreous.

(2) That a single injection of purified penicillin does little harm and will control susceptible infection if given within twelve hours and will maintain bacteriostasis up to at least 24 hours. Multiple injections cause serious intra-ocular damage.

(3) That local application of drops or ointment will not pass penicillin into the aqueous in normal eyes but do so where the cornea is inflamed or traumatized.

(4) That iontophoresis, constant corneal baths and subconjunctival injections will maintain bacteriostatic levels in the aqueous especially in the presence of inflammation.

(5) That intra-muscular and intra-vitreous injections of penicillin do not produce bacteriostatic levels in the aqueous or vitreous and will not control experimental susceptible inflammation there.

In applying the lessons of these experimental results to the treatment of intra-ocular infection in man it was decided to determine the value of subconjunctival injections, for this was a method which appeared to be a useful adjuvant to local penicillin therapy and at the same time less dangerous than direct intra-ocular injection.

The value of the time factor and the presence of previous inflammation on the absorption of penicillin should be borne in mind.

It was necessary to prove that penicillin could be caused to reach the interior of the human eye in bacteriostatic amounts after subconjunctival injections before this method could logically be employed in therapy.

Experimental technique

Selected eyes were either hopelessly blind and due for removal or required conservative operation.

Four thousand Oxford units of sodium penicillin in normal saline were injected beneath the conjunctiva in the infero-lateral or infero-medial intermuscular quadrant about 8—10 mm. from the limbus. Previous anaesthesia was by 4 per cent. cocaine drops but these did not entirely prevent transitory stinging sensations in certain cases. Skin preparation was by 1 :2,000 neutral proflavine application and after the injection the eye was irrigated with warm saline to remove any penicillin which might have leaked back along the track of the needle. After the desired interval of 15, 30 or 60 minutes the eye was again irrigated and aspiration of the media was carried out by a fine (23 S.W.G.) hypodermic needle passed obliquely through the cornea or sclera or sclerotomy wound; 0·12 c.c. aqueous or vitreous was then withdrawn and immediately subjected to penicillin assay by the following method :—

Penicillin assay by Major G. D. Cunningham, M.B.E., R.A.M.C.

An approximate assay of the amount of penicillin present in the aqueous and vitreous was performed by the " agar-cup " method described by Garrod and Heatley[21]. Blood agar plates were poured with agar bases. Subsequent to inoculation with a 6 hour broth culture of the Oxford strain of staph. aureus, holes were made in the agar with a cork-borer. The blood agar was lifted out with a platinum loop, leaving a thin layer of agar in the base of the " cup." The fluids for examination were introduced into the cups by means of a syringe fitted with a hypodermic needle and in every case the amount introduced was about 1/30 c.c. In each case the penicillin which had been used for subconjunctival injection was also checked for potency by the same method.

For the purpose of assay varying dilutions of a freshly prepared solution of penicillin were tested by the same method and the width of inhibition measured. The dilutions were made with a phosphate-buffer solution of p H 6.8. In all, three batches of penicillin were tested, two manufactured by Pfizer and one by Squibb and the estimation was performed in duplicate.

A graph was drawn from an average of the above results and the concentration of penicillin in the aqueous and vitreous calculated directly from the graph. Proflavine was found to have a very slight inhibitory action on the Oxford type of staph. aureus, but when mixed in equal quantities with penicillin did not significantly reduce the inhibitory action of the latter.

Discussion

The series is of necessity small, owing to the fact that suitable human material is not readily available. From the data, however, it would appear that penicillin can be constantly absorbed into the aqueous following subconjunctival injection. Absorption into the

vitreous has occurred in 3 cases out of 6. Of the remaining two it is possible that the short time elapsing between the subconjunctival injection and the removal of the vitreous (15 minutes) was responsible for the failure of absorption in one case. In this connection it is interesting to note that in his series of rabbit eyes Leopold[12] obtained no absorption into the vitreous under 30 minutes. In the other case (case 8) there was considerable disorganisation of the eye and this may account for the lack of absorption.

The following table summarises the results obtained.

Observations on experimental results

It will be seen from the table that after a subconjunctival injection of 4,000 O.U. sod. penicillin the drug penetrated to the aqueous humour in seven of the eight cases after an interval of fifteen minutes. The only negative case was probably due to the short interval of aspiration after injection.

Assay of the vitreous was carried out in six cases of which three cases showed bacteriostasis after forty-five minutes. Two of the three negative cases were examined 30 minutes or less after injection and this may account for the lack of inhibition.

All amounts of penicillin detected in aqueous or vitreous after subconjunctival injections were above bacteriostatic level.

Conclusion

(1) Subconjunctival injections of 4,000 O. units sod. penicillin will produce bacteriostasis of susceptible organisms in the aqueous humour of the human eye within half an hour of injection. It is probable that the same state of affairs is later attained in the vitreous humour and is likely to remain so for at least twenty-four hours.

(2) Subconjunctival injections of penicillin represent a practical method of causing penicillin to reach the interior of the eye. They have been widely employed in this Theatre without harmful effects and the earlier they are employed, the better the results.

(3) Large doses should be employed not only because of the slow rate of diffusion but also to avoid the risk of producing penicillin resistance (18) (19).

Florey[20] has written " Penicillin must be kept continuously in contact with all infected tissues until the natural body defences have had time to deal with the infection." It is therefore probable that the best results of penicillin therapy for deep intra-ocular infection will be obtained by a combination of routes and of these the subconjunctival method is practicable and harmless. Experimental evidence stresses the importance of bringing the drug in contact with the invading organism at the earliest possible stage.

RESULTS OF 10 CASES

No.	Name	History	Date	Penicillin Subconjunctival Injection	Aspiration Interval after Injection	Aqueous Assay of Penicillin		Vitreous Assay of Penicillin		Control	Comment
						Area of Inhibition	O. Units per c.c.	Area of Inhibition	O. Units		
1.	Y.	Old complete detachment of retina. R.E. A.C. aspiration	May 2, 1945	4,000 O.U. in 0·9 per cent. sterile saline	15 minutes	5 mm.	3	Not taken	Not taken	17 mm.	Aqueous inhibition after 15 minutes
2	O'H.	Sarcoma of the choroid. L.E. enucleation. Aqueous and vitreous aspiration	May 6, 1945	ditto	60 minutes	7 mm.	10	11 mm.	>20	16 mm.	Both aqueous and vitreous inhibition after 60 minutes
3	P.	Absolute glaucoma due to childhood injury. R.E. enucleation. Aqueous and vitreous aspiration	May 10, 1945	ditto	30 minutes	3 mm.	1	Negative. No inhibition	Nil	17 mm.	No vitreous inhibition after 30 minutes
4	B.	Acute bilateral iridocylitis and secondary glaucoma due to multiple penetrating wounds of both eyes. (Schu mine). R. L. aqueous aspirations	May 10, 1945	R.E. 4,000 O.U. in 0·9 per cent. sterile saline. L.E. control (nil)	30 minutes	R. E. 8 mm. L. E. nil	R.E. 15 L.E. nil	R.E. not taken. L.E. not taken	Nil Nil	17 mm.	R. E. aqueous inhibition. L.E. was control and was negative
5	C.	Penetrating transverse wound of both orbits. Loss of right eye. Avulsion of L. optic nerve. L.E. aqueous aspiration	May 9, 1945	4,000 O.U.	30 minutes	3 mm.	1	Not taken	Not taken	13 mm.	Aqueous inhibition after 30 minutes

RESULTS OF 10 CASES—*continued*

No.	Name	History	Date	Penicillin Subconjunctival Injection	Aspiration Interval after Injection	Aqueous Assay of Peniciilin		Vitreous Assay of Penicillin		Control	Comment
						Area of Inhibition	O. Units per c.c.	Area of Inhibition	O. Units		
6	S.	Absolute glaucoma R.E. Aqueous aspiration	May 14, 1945	4,000 O.U.	30 minutes	4 mm.	2	Not taken	Not taken	16 mm.	Aqueous inhibition after 30 minutes
7	K.	Penetrating wound L.E G.M. extraction of I.O.F.B. Vitreous aspiration through scleral incision	May 20, 1945	ditto	45 minutes	None	None	8 mm.	15	14 mm.	Marked vitreous inhibition after 45 minutes
8	V.	Penetrating wound R.E. Phthisis bulb. R.E. enucleation. Aqueous and vitreous aspiration	May 31, 1945	ditto	90 minutes	9 mm.	20	Negative. No inhibition	—	14 mm.	Aqueous inhibition but no inhibition of vitreous after 90 minutes
9	P.	Penetrating wound R.E. G.M. extraction of I.O F.B. Vitreous aspiration through sclerotomy incision	May 31	ditto	90 minutes	None taken	—	7 mm.	10	14 mm.	Vitreous inhibition after 90 minutes
10	H.	Absolute glaucoma from old penetrating injury. R.E. enucleation. Aqueous and vitreous aspiration	May 18	ditto	15 minutes	Negative	—	Negative. No inhibition	—	15 mm.	This case was completely negative for aqueous and vitreous inhibitions after 15 minutes

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PENICILLIN IN OPHTHALMOLOGY*

An interim review

BY

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1.—Ocular pharmacology of penicillin

Tolerance

PENICILLIN in current clinical use is adequately standardised as regards potency, but is still largely an impure product so that a final assessment of the ocular tolerance to this drug as distinct from the available mixtures, is not possible at the present. The following data must therefore be treated with some reserve,

* Based on a lecture delivered at the Royal College of Surgeons, May 29, 1945.

though they may be taken to apply to the penicillin in current use (which contains only 10—20 per cent. of pure penicillin).

(*a*) *Application to the conjunctiva and cornea.*—In the rabbit drops of the isotonic saline solution of sodium penicillin in a concentration of 10,000 units per c.c. instilled every 5 minutes for an hour produced no obvious discomfort nor any objective evidence of irritability or damage to the corneal epithelium (as determined by fluorescein staining and examination with the slit-lamp.) In contrast there were a number of stained areas 18 hours after a single instillation of drops of penicillin in a concentration of 20,000 units per c.c. In man drops in a concentration of 5,000 units per c.c. are well tolerated by most patients, though some complain of a stinging sensation when the drops are first instilled, whilst repeated application produces some reddening of the conjunctiva in most patients. In contrast drops in a concentration of 2,500 units are generally well tolerated.

Sodium penicillin can be instilled in the form of lamellae containing 250 units, but the base appears to be of some importance. Gelatine lamellae do not dissolve readily, whilst Parke Davis oculets which dissolve almost instantaneously invariably produce a transitory stinging sensation. Lamellae made of lactose (Neely & Cross, 1945) dissolve less readily, but it has still to be established that penicillin so instilled persists in the conjunctiva longer than drops do.

(*b*) *Subconjunctival injection.*—In the rabbit subconjunctival injection of sodium penicillin in doses of 2,500 and 5,000 units dissolved in 0·25 c.c. of water produces no irritation. The yellowish subconjunctival bleb is readily absorbed, leaving no trace of discoloration or irritation after 18 hours. In man 1,250 units injected in 0·5 c.c. of isotonic saline produces a transitory stinging sensation; after 24 hours there is considerable conjunctival hyperaemia over an area somewhat larger than the original bleb. A second injection at this stage is distinctly painful, but after three days is almost as well tolerated as the original injection. Injections containing 5—600 units are well tolerated, and can be repeated daily without much discomfort.

(*c*) *Injection into the anterior chamber.*—In the rabbit injection of 200 units of penicillin in 0·2 c.c. of isotonic saline into the anterior chamber is fairly well tolerated. Within 24 hours there is some exudative reaction at the pupil margin—distinctly more than the mild reaction noticeable with almost any injection into the animal's anterior chamber. This reaction is transitory and within 3 days it leaves no trace.

In contrast injection of 2,000 units leads to a marked iritis.

(It is not easy to be sure of the actual amount injected, as almost invariably there is some leakage from the puncture wound.)

(*d*) *Intravitreal injection.*—In the rabbit the control eye into

which 0·2 c.c. of sterile water had been injected, may show no changes or a definite vitreous opacity. The injection of 375, 750, 1,500 and 2,000 units of sodium or calcium penicillin dissolved in 0·2 c.c. of water or isotonic saline is badly borne. The smaller amounts produce gross yellow vitreous opacities whilst with 1,500 units dense yellow fibrous bands develop within a week; in two out of six eyes thus treated the process continued till the globe became a shrunken mass.

For three or four days after the injection the vitreous is generally too hazy to allow any fundus details to be observed. Subsequently the opacity is more localized and gross fundus disturbances downwards (apparently from penicillin dripping down) are noticeable. In 2 eyes a white area or atrophy simulating a typical choroidal coloboma was observed.

Substantially similar results are reported by other observers in the scattered and occasionally indirect literature.

(*a*) *Tolerance of the conjunctiva and cornea.*—According to Struble and Bellows (1944) drops containing penicillin in a concentration of 20,000 units per c.c. are well tolerated by the rabbit eye; in man the use of a concentration of 10,000 units per c.c. produced no corneal damage. A concentration of 10,000 units per c.c. was used by Keyes (1944) with good result at 2-hourly intervals for 7 days. Penicillin in ointment form 500 units per gram of Lanette Wax S.X. was found superior to drops in a concentration of 500 units per c.c. by Crawford and King (1944), but Milner (1944) found Lanette Wax ointment containing 100 units per gram more irritating than drops of 500 units per c.c. In [?] one case Rycroft (1945) used penicillin in powder form at 3-hourly intervals with apparently good tolerance, whilst Juler and Young (1945) used sodium penicillin in crystal form for septic ulcers of the cornea.

(*b*) *Tolerance to subconjunctival injection.*—In the rabbit subconjunctival injection of penicillin in doses up to 2,500 units dissolved in 0·25 c.c. of isotonic saline is well tolerated, but some chemosis develops on the injection of 5,000 units (Struble and Bellows, 1944). In man La Rocca (1945) gave daily subconjunctival injections in progressively increasing doses, ranging from 50 to 1,000 units.

(*c*) *Tolerance to injections into the anterior chamber.*—Clinical use of penicillin instilled into the anterior chamber is reported by Cashell (1944), Grant (1944), La Rocca (1945), Mietus (1945) and Rycroft (1945). Cashell irrigated the anterior chamber in two cases of perforating injuries [? leaving one drop of penicillin in a concentration of 500 units per c.c.]. Grant, La Rocca and Mietus each report single cases in which about 50 units of penicillin were introduced with good results into the anterior chamber

in perforating injuries. In no case was it necessary to repeat the injection. (La Rocca "forced" 50 units into the anterior chamber; Grant and Mietus introduced 0·25 c.c. of a solution containing 250 units per c.c.) Rycroft replaced 2 minims of aqueous by an equal quantity of water containing 2,000 units of penicillin; this procedure was carried out in 2 patients and was well tolerated.

(*d*) *Tolerance of the vitreous to penicillin.*—Von Sallmann, Meyer and Grandi (1944) report that 0·2 c.c. of a solution containing 2·5 mgr. (approximately 250—375 units) of highly purified penicillin (*i.e.*, a total amount of 50—75 units) produced a slight and transitory reaction on injection into the vitreous. Crude penicillin was more irritating, and more readily produced visible fundus changes seen histologically as damage to the retina. A second injection greatly increased the damage, the lens also becoming affected. On the other hand Rycroft (1945) holds the injection of 2,000 units (dissolved in 2 minims of water) into the vitreous was well tolerated in 3 patients, as was an injection of 5,000 units in a single case. The report by Leopold (1945) on the effect of penicillin in experimental infections of the vitreous suggests that the infected rabbit eye tolerates concentrations as high as 2,500 units.

Concentration in ocular tissues

Tears: In man no penicillin has been detected in the tears when the drug is injected intravenously, intramuscularly or subcutaneously (Rammelkampf and Keefer, 1943). A similarly negative finding is reported for the cat by Florey and his associates, but Struble and Bellows found penicillin in the tears of dogs which had received a massive intravenous dose.

1. *Concentration in the eye after systemic injection of penicillin.*—In rabbits the injection of 20mgs. (approximately 2—3,000 units) of penicillin per kilo of bodyweight, produces a very much lower level of concentration in the aqueous compared with the blood concentration, and there was no inhibitory effect on bacteria in the aqueous withdrawn after 15 minutes; primary aqueous at 30 and 45 minutes showed moderate antibacterial action; secondary aqueous withdrawn 45 and 60 minutes after injection (and 30 minutes after the first paracentesis) showed a distinctly higher concentration of penicillin. No antibacterial activity was noted in the vitreous (as also in cerebro-spinal fluid) taken 45, 60 and 75 minutes after the injection of penicillin (v. Sallmann and Meyer, 1944). Leopold and La Motte (1945) could not detect any penicillin in the aqueous of rabbits examined 15, 45 and 105 minutes after intramuscular injection of 1,500 units per kilo of bodyweight.

In the dog Struble and Bellows (1944) found that penicillin

reaches the ocular tissues readily after a single massive dose (12,800 units per kilo of bodyweight). Within 15 minutes the penicillin was at its highest concentration in the chorio-retinal tissues and extra-ocular muscles. In the less vascularised tissues (conjunctiva, cornea and sclera) and in the aqueous there was an initial sharp rise within the first 15 minutes and concentration continued to increase slowly until the end of the 1st hour. Barely a trace of penicillin remained in the eyeball after 3 hours. The concentration of penicillin in the tissues, listed in decreasing order was: extra-ocular muscles, sclera, conjunctiva, tears, chorio-retinal layer, aqueous, vitreous and cornea; there was none in the lens. When these observers used a dose more nearly that used in clinical work, they found no antibacterial activity in the blood tested at hourly intervals, and in the ocular tissues tested at the end of 3, 4, 5 and 6 hours after slow intravenous drip, or several intramuscular injections.

Leopold (1945) could not detect any penicillin in the vitreous of rabbits that had been given 4,000 units per kilo of bodyweight. The injections were made intramuscularly and intravenously, and the determinations of vitreous concentration carried out at intervals ranging from 15 minutes to 4 hours; the addition of gelatin and a vasconstrictor substance to the intramuscularly injected penicillin did not produce any effect, though there was a slower excretion of penicillin from the body. The preliminary injection of histamine into the vitreous produced a barely perceptible concentration of penicillin in two out of 12 experiments and a somewhat higher concentration in some of the rabbits whose anterior chambers had previously been grossly infected by the introduction of staphylococci.

Rycroft (1945) gives the following data on man: 1,500 [? 15,000] units of penicillin were injected intramuscularly in 2 c.c. of water administered every 3 hours. Five patients were moribund, and the tests for the presence of penicillin in the eyes were carried out 35, 19, 7, 4 and 6 hours after the last administration. In none of these patients did the aqueous or vitreous show any antibacterial activity. (The last two patients in this series had received 390,000 units in several doses and 30,000 units in one dose respectively, and their eyes had been removed 3 hours and 2 hours respectively after death.) In two moribund patients with grossly injured eyes, essentially negative results were likewise obtained when a penicillin assay was done 13 hours and 3 hours after the last dose, though it is worth noting that in this last case, which had received a single large dose of 30,000 units, slight bacteriostasis is reported for both the aqueous and vitreous. In 5 more patients with injured eyes which were excised (the patients' general condition being good) the aqueous and vitreous were tested in 2 cases ½ hour, in 2 more 1 hour and in 1 case 2 hours after the last

injection. Here too no anti-bacterial effect was seen in the aqueous and vitreous. All these patients had received 30,000 units of penicillin in 2 doses at an interval of about 2 hours.

2. *Concentration after local application.*—1. Application of drops. Von Sallmann and Meyer (1944) obtained "erratic results" in 2 instances, and in 4 experiments no inhibitory activity of the aqueous could be detected. Leopold and La Motte (1945) report to the same effect. Struble and Bellows (1944) introduced into the conjunctival sac an excess of solution containing 20,000 units of penicillin per c.c. of isotonic saline; "the lids were clamped sufficiently tight to prevent an escape of the fluid." The penicillin penetrated readily through the cornea and the aqueous showed a value of 3·32 units per c.c. in 30 minutes, a level maintained with but little change for 1½ hours, but increasing to 14·2 units per c.c. by 3 hours. The concentration of the drug in the cornea, iris and ciliary body was also high. The following table from Bellows (1944) gives the essential data:—

Concentration of Penicillin in the globe after constant corneal baths. (20,000 units per c.c.)

	Concentration in Oxford Units per gr. or c.c.		
	0·5 hour.	1 hour.	3 hours.
Aqueous	3·32	4·18	14·2
Conjunctiva	114·11	177·63	26·34
Cornea	46·23	90·42	27·47
Iris and Ciliary Body ...	30·49	35·0	9·18
Vitreous	0·92	1·95	Trace
Sclera	39·76	57·13	?
Posterior uvea and retina	Trace	Trace	?

There was no penicillin in the lens, but some could be detected in the vitreous. It should be noted that depletion from the anterior chamber is considerably slower than from the blood—a point also brought out by v. Sallmann and Meyer.

2. Application of ointments. V. Sallmann and Meyer, who could not obtain any bacteriostatic effect with the aqueous of rabbits receiving penicillin in drop forms, were also unable to obtain any results when ointments instead of drops were used. Leopold and La Motte likewise did not find ointments any more effective than drops.

3. Subconjunctival injections. The level of penicillin in the various ocular tissues is high when the drug is introduced subconjunctivally. For the anterior segment of the eye it is many

times higher than that obtained by the intravenous route or by local application. One and a half to 3 hours after subconjunctival injection of 2,500 units the following values were obtained by Struble and Bellows.

Cornea: 28 units per gr. Vitreous 1·95 units; iris and ciliary body 10·8 to 26·3 units; sclera as a whole 163·2 to 194·7; posterior part of sclera 92·5 to 93·3; conjunctiva 106 to 449. After 3 hours most of the ocular tissues tested were essentially negative except for slight amounts in the aqueous and vitreous humours.

Leopold (1945) gives the following values:—

When 2,500 units of penicillin (in 0·25 c.c. of isotonic saline) are injected subconjunctivally in the rabbit penicillin could not be detected in the vitreous 15 minutes after the injection; 0·078 units per c.c. was present 30 minutes later, and the same values were obtained 105 and 180 minutes after injection. Considerably higher values were found if the anterior chamber had first been grossly infected by injection of staphylococcus aureus (0·128, 0·510, 0·250 and 0·250 units per c.c. 15, 45, 105 and 180 minutes respectively after subconjunctival injection).

4. Injection into the anterior chamber. No data appear to be available on the date of excretion of penicillin injected into the anterior chamber, but Leopold (1945) has shown that the concentration in the vitreous at 15, 45, 105, 180 and 240 minutes after injection of 500 units (in 0·25 c.c. isotonic saline) into the anterior chamber is much higher than that obtained by the injection of 2,500 units subconjunctivally. The highest concentration was at 105 minutes after injection. In rabbits that had undergone a broad iridectomy the concentration—initially the same—tended to increase after 105 minutes. A distinctly higher concentration in the vitreous was obtained in rabbits with grossly infected anterior chambers.

5. Injection into the vitreous. When 0·2 c.c. of a solution of penicillin containing 2·5 mg. per c.c. (2,500 units per c.c.) is injected into the vitreous a high concentration was still present at the end of six hours (between 180 to 480 microgram per c.c.); at 12 hours the concentration had declined to 45 to 67·5 micrograms per c.c.; after 24 hours it had declined to 45 micrograms—almost 4 times the concentration needed to inhibit the growth of a test-tube sulture of pneumococcus type III in a dilution of 10^{-4} (v. Sallmann, Meyer and Di Grandi, 1944). (Intravitreal injection of sodium sulphacetamide also maintained high levels of concentration.)

In a case recorded by Rycroft (1945) there was still a " high concentration of penicillin " 2 days after 5,000 units had been injected.

6. Instillation into the conjunctival sac: effect of (*a*) modifying

factors (wetting agents, corneal baths, iontophoresis, ointment bases) and (*b*) corneal abrasion and ulcer.

(*a*) Wetting agents do not increase the penetration of penicillin through the cornea into the aqueous (v. Sallmann and Meyer). A corneal bath is, however, effective (v. Sallmann and Meyer, Struble and Bellows), and iontophoresis still more effective, both in producing higher concentrations of penicillin in the anterior chamber and in maintaining these higher levels. When ointments are used the base is of importance, as the following table from Bellows (1944) shows:—

Effect of various bases upon the penetration of penicillin through the cornea. (25,000 units per gram base.)

	Simple Ointment	Oil-in-water Emulsion	"Vanishing" type Stearate	Lubricating Jelly
Penicillin in aqueous after 1 hour ...	0·42	0·38	3·43*	0·05

* Damage to corneal epithelium.

(*b*) In the presence of a corneal abrasion or ulcer penicillin penetrates readily through the cornea into the anterior chamber. Aqueous withdrawn 15, 45 and 105 minutes after the intramuscular injection into rabbits of 1,500 units per kiloweights show the following concentrations respectively: 0·4, 0·15 and 0·15 units per c.c. if there is an experimental corneal lesion against none in animals with normal corneae. Somewhat similar results are obtained with local applications: In the intact animal the aqueous shows no antibacterial action when withdrawn at 15, 45 and 105 minutes after instillation of drops (500 units per c.c.) or ointment (500 units per gram). When the corneae are abraded, drops give the following concentrations in the aqueous at the times indicated: 1·5, 1·5 and 0·6 units per c.c.; inflamed corneae give a somewhat lower concentration; solutions give a higher aqueous concentration than ointments (Leopold and La Motte, 1945).

2.—Penicillin in experimental infections

1. *Corneal infections.*—Robson and Scott (1943) report on the use of penicillin in experimental corneal lesions produced in the rabbit by a strain of staphylococcus aureus and by pneumococcus type XIX. Leopold, Holmes and La Motte (1945) studied the effect of penicillin both by local application and by intramuscular injection in corneal infection due to a bacillus allied to the Friedlander bacillus.

Staphylococcal infections. Penicillin [? concentration] was instilled 1 hour after infection and continued hourly for 48 hours

and thereafter hourly during the day only. Fourteen out of 17 eyes treated suffered slight or negligible damage, against moderate or severe damage in all but one of the control eyes. When treatment was started 24 hours after the infection, it was almost without effect.

Pneumococcal infections. Penicillin was instilled hourly for 36 hours and then hourly by day for about 3 days. Twenty-two of 28 eyes treated within 1, 6 or 12 hours after infection showed only very slight or slight lesions, against severe lesions in all the untreated eyes. Even when treatment was started at 24 hours there was some effect—8 out of 14 lesions were slight, while the lesions in all the control eyes were severe.

Infection due to a gram-negative rod simulating the Friedlander bacillus, but sensitive to penicillin in vitro:—

(*a*) Twelve rabbits were treated 2 hours after the infection by penicillin drops having a concentration of 500 units per c.c. applied hourly for 11 hours on the first day and after a treatment-free interval of 11 hours again hourly for a further 13 hours. On the third day penicillin was instilled only 4 times during the 24 hours.

(*b*) Three rabbits were treated by intramuscular injection of 250 units per kilo of bodyweight. The injections were begun 2 hours after the infection and were given at 2 hourly intervals for 3 days, except during the 8 hours after midnight.

The untreated eyes and the eyes of the three rabbits treated by intramuscular injections all showed severe lesions, in contrast to barely perceptible reactions in the eyes treated by local applications.

A similar experiment carried out with the first treatment delayed for 24 hours gave essentially the same results. The untreated eyes and the eyes of rabbits treated by intramuscular injections showed severe lesions, whilst the eyes treated locally did much better, though not so well as those in the first series (in which treatment was begun 2 hours after the infection).

2. *Inoculation into the Anterior Chamber.*—1. Pneumococcus. V. Sallmann (1943) reports on infection with pneumococcus types 3, 7 and 10. Penicillin in solutions 0·1 per cent. and 0·25 per cent. was applied by corneal baths and iontophoresis; higher concentrations were found to damage the corneal epithelium. In general 0·05 c.c. of a 10^{-4} dilution of a 24 hours broth culture was injected into the anterior chamber. Treatment was started 6 and 12 hours after inoculation. Pneumococcus type VII gave the most violent initial reaction.

Type III. Five eyes treated six hours after inoculation and continued for 2 days (the treatment being sodium penicillin applied by iontophoresis or by corneal bath) all recovered (in contrast to six eyes, all lost, when treated by sodium sulphadiazine iontophoresis and sulphadiazine feeding, and 5 control eyes, also all

lost). Eleven out of 12 eyes first treated 12—13 hours after inoculation also recovered (against 2 out of 3 controls). Nine out of 12 eyes in which the lens was deliberately injured at the time of inoculation recovered when treated after 6 hours (against none of 3 controls).

Type X. Six eyes treated within 6 hours of inoculation all recovered (against 1 out of 12 controls, six of which had received sodium sulphadiazine iontophoresis and sulphadiazine feeding and 4 sulphadiazine feeding only). Five out of 6 eyes first treated 12—13 hours after inoculation also recovered (against none out of 2 controls). When the lens was also injured, none of the three control eyes recovered, but the 9 treated eyes all recovered with treatment begun after six hours.

Type VII. Treatment begun in 12 eyes 12—13 hours after inoculation led to recovery in 9 eyes; the 4 controls were all lost.

2. Staphylococcus aureus. Inoculating 0·05 c.c. of a 10^{-4} culture of strains of staphylococcus aureus into the anterior chamber and at the same time deliberately injuring the lens, von Sallmann (1944*a*) obtained 15 recoveries in 24 infections by the use of sodium penicillin iontophoresis begun 6 to 7 hours after infection. The 19 control eyes were all lost, as were 12 out of 13 eyes in rabbits treated by the oral administration of sulphadiazine, and 18 out of 23 when sulphadiazine feeding was combined with sodium sulphadiazine iontophoresis. In a further series (v. Sallmann 1944b) there were 9 recoveries out of 12 eyes, and no better results could be obtained by combining local penicillin therapy with sulphadiazine iontophoresis and feeding.

3. Cl. Welchii. Intralenticular injections of this organism in 8 eyes gave a destructive endophthalmitis not influenced by local penicillin therapy (nor by combined sulphadiazine therapy in 4 more eyes, and in 12 untreated control eyes). (v. Sallmann, 1944*a*.)

3. *Inoculation of staphylococcus aureus into the vitreous.*—The injection into the vitreous of 0·05 c.c. of a 24 hours broth culture of staphylococcus aureus in a dilution of 10^{-4} or 10^{-5} (v. Sallmann, Meyer and Di Grandi, 1944) induced a destructive suppurative endophthalmitis in the rabbit, sometime fulminating and at times more slowly leading to the development of a vitreous abscess within 4 to 7 days. Histologically dense leucocytic infiltration with much destruction of the retina together with exudative retinal detachment were present within 30 hours of the infection. Twenty control eyes were all lost, as were all the 8 eyes treated within 6 hours by an intravitreal injection of 0·2 c.c. of 10 per cent. solution of sodium sulphacetamide. In contrast 10 eyes treated within 6 hours by either one or two intravitreal injections of 0·2 c.c. of sodium penicillin in a concentration of 2,500 units per c.c. (i.e.

500 units per injection), all recovered, as did 10 eyes first treated likewise 12 hours after the infection; 10 eyes in which treatment was begun 24 hours after the infection were all lost.

Though penicillin controlled the infection it appeared to have a somewhat deleterious effect on the vitreous, retina and lens, this effect being more marked with 2 intravitreal injections than one.

Earlier v. Sallmann (1943) had noted that penicillin iontophoresis did not check pneumococcal infection introduced into the anterior chamber, once the process had spread backward to the vitreous.

Leopold (1945) reports a comparative study on the effect of penicillin administered by different routes in experimental standard infection of the vitreous by staphylococcus aureus.

0·01 c.c. of a diluted 18 hours broth culture of staphylococcus aureus containing approximately 400 organisms was injected into each of the two eyes in 50 rabbits. Severe infection developed within 24 hours; the vitreous gradually became opaque and all untreated eyes were phthisical within 4 to 6 weeks. Where treatment was given it was started 2 hours after the inoculation.

(*a*) Intravenous administration of 4,000 units of penicillin per kilo of bodyweight: carried out in 6 rabbits at 2 hourly intervals for 72 hours. No therapeutic effect.

(*b*) Subconjunctival injection of 2,500 units in 0·25 c.c. of isotonic saline: carried out every 3 hours for 72 hours in the right eye of 6 rabbits. The six control eyes and 4 of the treated eyes were lost; the remaining 2 eyes showed partial control of the infection.

(*c*) Injection into the anterior chamber of 500 units of penicillin at 3 hourly intervals for 72 hours in the right eye of 6 rabbits. The six control eyes and 4 of the treated eyes were lost; the remaining two gave a fair response.

(*d*) Intravitreal injection of 2,500 units of penicillin: carried out once in the right eye of six rabbits. The six control eyes were all lost. All the six treated eyes were quiet after 4 weeks of observation, showing nothing beyond occasional vitreous opacities.

(*e*) Intravitreal injections of penicillin in quantities less than 2,500 units: 2 eyes received 2,000, 1,000, 500, 250, 50, 25, 10 and 5 units each and 4 eyes 100 units each. All eyes receiving more than 1,000 units were as favourably influenced as those receiving 2,500 units, but only 2 eyes with lower dosage (one with 500 and one 250 units) responded as satisfactorily; yet even in the poorest result the beneficial effect of penicillin was obvious.

3. Clinical experiences

1. Systemic administration.—As yet only a few reports are available. The following summary table shows the essential data:

Author	Clinical condition	Treatment	Result	Remarks
Mietus, 1945	Pellet injury to eye with retained F.B. Threatened panophthalmitis	25,000 units every 3 hours for 42 days	Recovery	—
Green and Jakobowits, 1945	Suppurative endophthalmitis following cataract operation 4 years previously, complicated by prolapse of iris. Staphylococcal infection	20,000 units intramuscularly every 3 hours. Total: 22 injections	Recovery	Case had proved refractory to sulphonamides
Rycroft (*a*) 1945	War injury. 10 F. Bs. extracted with magnet. Hypopyon with yellow retrolenticular reflex 2 days later	15,000 units intramuscularly every 3 hours. Total: 500,000 units.	No improvement	When intramuscular course completed 30,000 units injected into aqueous. No response. Finally improved after a course of sulphathiazole
—— (*b*)	War injury. Infected penetrating wound of cornea. Hypopyon	15,000 units intramuscularly every 3 hours. Total; 500,000 units	No improvement	Preliminary sulphathiazole and T.A.B. therapy without result
Griffey, 1944	Gonococcal conjunctivitis in a man aged 24 years	25,000 units intramuscularly every 3 hours. Total: 10 injections	Rapid recovery	Previously treated with sulphathiazole when urethritis cleared, but not the conjunctivitis
Dunnington and v. Sallmann (also reported by Elliott), 1944	Severe plastic iritis developing in the course of sulphadiazine treatment of gonorrhoea	15,000 units intravenously every 3 hours for 5 days	Marked improvement in 48 hours. Total recovery in 14 days	Localapplication of penicillin by ionization also carried out

Author	Clinical condition	Treatment	Result	Remarks
Sievers et al. 1944	Eight cases of ophthalmia neonatorum, 2 being gonococcal	10,000 units intramuscularly every 3 hours: Total dosage:— 1 case 60,000 units 1 case 120,000 units *1 case 230,000 units 1 case 240,000 units *1 case 330,000 units 3 cases 180,000 units	Six cases (unstarred) responded well within 24 hours	The 2 failures showed some improvement originally, but relapsed
Bellows (*a*) 1944	Two cases of chronic exudative choroiditis	Massive doses of penicillin parenterally and locally	No response	—
—— (*b*)	Gonococcal iridocyclitis	—		—
Berens (*a*)	Choroiditis	—	No response	—
—— (*b*)	Iridocyclitis			
Somerville-Large, 1945	Iridocyclitis	—	No response	—
Goldberg 1945	One case gonorrhoeal choroiditis Five cases of choroiditis—probably tuberculous	160,000 units daily for 3 days ? same dose	Good response No response	—
Brücher (*a*) 1944	Severe endophthalmitis following septic abortion	15,000 units intramuscularly every 3 hours for 3 days. Total: 400,000	—	Preliminary sulphathiazole therapy no response. Rapid recovery under penicillin, giving vision of 0·8. Subsequently retinal detachment developed. Operation only partially successful
—— (*b*)	*ibid.*	On same lines as (*a*)	—	Good result. Residual vision 0·3
—— (*c*)	*ibid.*	ditto	—	Good result. Residual vision 0·8
—— (*d*)	*ibid.*, "several cases"	ditto	—	No result

2. *Intravitreal injections.*—The only records available are those reported by Rycroft, who used this procedure in 4 cases.

1. Penetrating injury of cornea from barbed wire. Two days later there was infection of the corneal wound, hypopyon, iritis

and local lens changes. A course of sulphathiazole and shock therapy produced some improvement; a subsequent course of 500,000 units of penicillin intramuscularly gave no further improvement. Intravitreal injection of 2,000 units of sodium penicillin did not save the eye from enucleation.

2. Penetrating scleral wound from explosion of a Mills grenade. Two days later this was covered by a conjunctival flap at a casualty clearing station; six days after this the eye showed acute iritis and a yellow vitreous reflex. There was no P.L. and radiography showed an intra-ocular foreign body, which was removed the following day; turbid vitreous escaped and 2,000 units of penicillin injected. "Normal convalescence; the eye settled and became white, but the yellow vitreous reflex persisted. Tension normal to soft and vision No. P.L." The vitreous and foreign body were both sterile.

3. Penetrating corneal wound from shell fragment. There was prolapse of iris, traumatic cataract and a large intra-ocular foreign body which was removed at a Mobile Unit. Six days later the vitreous showed gross infection and on the following day 5,000 units of sodium penicillin were injected into the vitreous. Two days after this the condition had so deteriorated as to call for excision of the eye; the vitreous was found sterile and still possessed a "high concentration of penicillin."

4. Limbal penetrating wound from splinter with iris prolapse. The iris prolapse was excised two days after the injury at a Mobile Unit. Seen 9 days after the operation, there was acute iritis, canary-yellow vitreous and an intra ocular foreign body, which was removed; an intravitreal injection of 2,000 units of penicillin was given. Three weeks subsequently: "eye quiet and white. Diffuse yellow reflex behind the lens infiltrating the vitreous. This appears to have increased since the operation. Tension soft. Vision faint P.L." Within a further fortnight the eye had to be excised because of pain and irritability; "globe shrinking rapidly." Both the vitreous and foreign body proved sterile.

3. *Penicillin introduced into the anterior chamber.*—La Rocca (1945) "forced" 50 units of penicillin into the anterior chamber of a patient suffering from a hypopyon ulcer resistant to sulphonamide and T.A.B. treatment (100 units were simultaneously injected subconjunctivally). On the following day the hypopyon had disappeared.

Cashell (1944) irrigated the anterior chamber with penicillin [? leaving one drop of a solution containing 500 units per c.c.] in one case of perforating injury and in another of post-operative (cataract) infection. Except for anterior chamber lavage (and local penicillin therapy) "these eyes would undoubtedly have been lost from panophthalmitis."

Grant (1944) and Mietus (1945) both report the replacement of

0·25 c.c. aqueous by 0·25 c.c. solution containing 250 units of penicillin per c.c. In Grant's case there was a penetrating wound with exudative iridocyclitis; recovery set in within 48 hours. In Mietus' case a perforating injury with prolapse of iris was followed by a severe iritis with hypopyon; 48 hours after the injection into the anterior chamber the eye was white.

Rycroft (1945) replaced 2 minims of aqueous by the same quantity of solution containing 2,000 units of penicillin. In one case of hypopyon keratitis there was no improvement; there was likewise no improvement in a second case of purulent infiltration of the cornea when penicillin solution was introduced into the aqueous and penicillin powder into the conjunctival sac. Both these cases had sustained war injuries.

4. *Subconjunctival injection.*—In a case of hypopyon keratitis treated by the injection of 50 units of penicillin into the anterior chamber, La Rocca added subconjunctival injections daily gradually working up to 1,000 units per injection. He also used subconjunctival injections, initially of 50 units but gradually working up to 1,000 units in a case of absolute glaucoma with hypopyon ulcer. In the first case there was no corneal staining after 11 days, and likewise none in the second after 22 days. The hypopyon had disappeared within 24 hours and 7 days in the two cases respectively.

5. *Local application of drops.*—A large number of reports on the value of penicillin in various external infections of the eye are on record.

1. *Ophthalmia neonatorum.*—(*a*) Florey and Florey (1943) used penicillin (6—800 units per c.c.) hourly during the day and 2 hourly at night in 5 cases: 2 showing staphylococcus aureus, 1 B. Coli, 1 gonococcus and 1 an undetermined organism. All responded well within a week.

(*b*) Lemoine and Lemoine (1944) used penicillin in a concentration of 700 units per c.c. at hourly intervals in 1 case showing staphylococci and streptococci, and obtained a cure within 3 days.

The gonococcal case in the series reported by the Floreys and the case recorded by the Lemoines had both previously been treated unsuccessfully by sulphonamides.

2. *Gonococcal ophthalmia.*—Bellows (1944) records a case of gonococcal ophthalmia in an adult cleared in 10 days by ½-hourly instillation of penicillin [? concentration].

3. *Acute conjunctivitis.*—Abraham *et al.* in 1941 and Florey and Florey in 1943 had already noted the value of penicillin in 3 and 4 cases of acute conjunctivitis respectively. Bellows (1944), Crawford and King (1944), Cashell (1944), Milner (1944), and Palin (1944), extended these observations by records on 22, 7, 10, 18 and an unspecified number respectively. Satisfactory results —cure within 12 hours to 10 days—were noted by all these

observers and the organisms involved were: staph. aureus, streptococci, Koch-Weeks bacillus and some unidentified. The concentration used ranged from 200—2,500 units per c.c. Crawford and King noted 1 relapse in their series of 7 cases, and Milner 2 relapses in 18 cases; one of Milner's cases showing staph. albus appeared to have been made worse.

4. *Subacute conjunctivitis.*—In a series of 19 cases—17 due to staph. aureus—recorded by Florey and Florey (1943) there was 1 failure; as an average it took 2½ weeks to produce cure with penicillin in a concentration of 600—800 units per c.c. Milner (1944) had 7 failures in 16 cases, some of these being non-organismal. Bellows (1944) obtained cure in 6 cases within 1—8 days.

5. *Acute conjunctivitis with superficial or marginal keratitis or corneal ulcer.*—Florey and Florey (1943), Crawford and King (1944), and Bellows (1944) report on 6, 12 and 3 cases respectively, and Mietus (1945) on a single case. The organisms met were chiefly staph. aureus, but included 2 cases showing diphtheroids (Crawford and King). With the exception of a relapse in one case of staph. aureus infection, the results were good (cure in about 7½—9 days in the series recorded by Crawford and King). The concentration used was generally 250 units per c.c.

6. *Corneal ulcer.*—(*a*) Simple ulcer. Abraham *et al.* in 1941 noted a good result in a single case of staphylococcal corneal ulcer. Cashell (1944) obtained cure in 4—18 days in 8 cases showing staph. aureus, one staph. albus and one more showing Bacillus of Petit; penicillin was used in a concentration of 500 units per c.c. Keyes ((1944) obtained a satisfactory result in two cases; a case with unidentified bacilli was treated with 250 units per c.c., and a case with staph. aureus by 1,000 units per c.c. Milner likewise had satisfactory results in 8 cases [? organism] using a concentration of 500 units per c.c. (or 100 units per gr. in ointment form).

(*b*) Dendritic ulcer. Milner (1944) could obtain no result in dendritic ulcer. Keyes (1944) observed improvement in 2 cases, but holds that this may have been due to hospitalization.

(*c*) Phlyctenular ulcer. Burr (1944) observed cure in 3 out of 4 cases treated with penicillin 500 units per c.c. (or 100 units per gram in ointment form). Recovery in 4 days, but with subsequent relapse, was noted in 1 case by Sampson (1944).

(*d*) Disciform keratitis. Negative results are reported by Milner.

(*e*) Recurrent marginal ulcer. In these too, Milner could obtain no results, but Dunnington and v. Sallmann obtained a cure in 5 days by the use of 0·5 per cent. sodium penicillin in ointment form at 3 hourly interval.

(*f*) Hypopyon keratitis. A satisfactory result is noted by the Floreys (1943) in 1 case treated with drops 600—800 units per c.c. (La Rocca, 1945, obtained a satisfactory result in 2 cases by the

use of subconjunctival injections, with the addition of an injection of 50 units into the anterior chamber in 1 case.) In a substantial study on 23 cases of septic ulcer of the cornea, mostly complicated by the presence of hypopyon, Juler and Young (1945) obtained gratifying results in all but 4 cases. The organisms found were pneumococcus (5 cases), staphylococcus aureus (7 cases), streptococcus (5 cases), Morax-Axenfeld Bacillus (3 cases), pneumobacillus (2 cases) and Bacillus pyocyaneus (1 case). They used penicillin drops in a concentration of 500 units per c.c. at hourly intervals during the day and 2 hourly at night; in some of their cases they curetted the ulcer and applied solid pencillin in crystal form.

7. *Blepharitis.*—The Floreys (1943, Cashell (1944), Milner (1944) and Crawford and King (1944) report on series of 46, 20, 26 and 19 cases respectively. The causal organism was generally staph. aureus, but single cases showing the Morax-Axenfeld bacillus are included by Crawford and King and by Milner. Recovery between 3 to 15 days is noted by these observers; penicillin was generally applied in the form of drops into the conjunctival sac. All observers, however, had some failures and relapses —an observation also made by Keyes. Florey, McFarlan and Mann (1945) report clinical recovery in 36 cases, improvement in 11 cases and failure in 1 case in a series treated by penicillin ointment containing 600—800 units per gram. Recovery generally took 3—10 weeks.

8. *Trachoma.*—Keyes (1944) obtained no result in a case of ? trachoma treated at 2 hourly intervals for 9 days by drops containing 1,000 units per c.c. Gilford (1945) found that 4 cases " subsided rapidly " under drops applied 3 hourly and containing 16,000 units per c.c. Milner (1944) and Bellows (1944) each report improvement in a doubtful case of trachoma.

9. *Episcleritis.*—A rapid response, followed by relapse, is noted in a case by Milner, who used penicillin in a concentration of 1,000 units per c.c. In 3 cases, Bellows found recovery in 24 hours once, and twice within a week.

10. *Infected socket.*—Satisfactory results are reported in single cases by the Floreys and Sampson. Burr likewise obtained a good result in 2 cases. Milner on the other hand found penicillin disappointing in several cases.

11. *Dacryocystitis.*—The Floreys obtained 3 successes in 6 cases by irrigation with penicillin 6—800 units per c.c. Milner injected the solution into the sac, whilst Cashell reports on 3 cases.

12. *Herpes ophthalmicus.*—Sampson (1944) obtained negative results.

13. *Post-operative infection.*—Dunnington and v. Sallmann (1944) applied penicillin locally in a case of incipient panophthalmitis noted on the first dressing of a cataract extraction in a

diabetic. The eye ultimately had to be excised. They also obtained no result in a post-operative infection in a Lagrange operation, also in a diabetic; penicillin in this case had been applied in a corneal bath.

6. *Personal experiences.*—1. *Penicillin in 85 cases of ophthalmia neonatorum.*—Initially drops in a concentration of 500 units per c.c. were used in 8 cases; only 3 recovered. When a concentration of 1,000 units per c.c. was used 4 out of 7 recovered, and with 1,500 units per c.c. 6 out of 10. When the concentration was increased to 2,500 units per c.c.—and the drops instilled at half-hourly intervals for 3 hours, then hourly for 24 hours and two hourly subsequently—21 cases out of 22 so treated recovered. None of these 21 cases took longer than 100 hours to show a clinical cure, and in 6 cases clinical cure was obtained within 3 to 24 hours.

Continuing the use of penicillin in a concentration of 2,500 units per c.c. a further 13 cases were treated with drops instilled at hourly intervals for 6 hours, then 2 hourly for 24 hours and subsequently at 3 hourly intervals; there was recovery in all cases in 4 to 60 hours, 4 of these cases showing clinical cure within 24 hours. There were, however, 2 relapses in this series. A final series of 25 cases was treated by intensive application of penicillin; drops were instilled at intervals of 5 minutes (no irrigation subsequent to the first one being found necessary) until all tendency to the formation of pus was suppressed; when all discharge had ceased penicillin was continued at half-hourly intervals till the eye was dry; thereafter it was instilled hourly for 12 hours and 2 hourly for a further 24 hours. In this series there were two failures, and 5 relapses after clinical cure, but of the cases that responded well no less than 13 showed clinical cure within 12 hours and a further 4 within 12—24 hours.

The following summary table shows the time taken for a clinical cure in the successfully treated cases of the 3 series, submitted to the same concentration of penicillin (2,500 units per c.c.) but at different time scales.

Penicillin drops in concentration of 2,500 units

	Initial Treatment		
	At 5 minutes intervals	At ½ hour intervals	At hourly intervals
Time taken for Clinical cure	Number of cases		
Within 12 hours ...	13	2	2
12-24 hours ...	4	4	2
24-48 hours ...	1	7	4
49-72 hours ...	–	3	3
Over 72 hours ...	–	4	–
	18	20	11

Average time per case: 10, 44 and 33 hours in the three series respectively.

The whole series of 60 cases treated by penicillin in a concentration of 2,500 units per c.c. is summarised in the two following tables, one showing the results in relation to severity and the other to causal organisms :—

At 5-minute intervals. 25 cases.	At half-hour intervals. 22 cases.	At hourly intervals. 13 cases.
MILD		
6 cases: Clinical cure in 25 minutes to 21 hours. Average: 8 hours. No failures. No relapses.	5 cases: Clinical cure in 7-78 hours. Average: 51 hours. No failures. No relapses.	3 cases: Clinical cure in 4 hours to 56 hours. Average: 36 hours. No failures. No relapses.
MODERATE		
13 cases: Clinical cure in 3 hours to 38 hours. Average (of 11 cases): 13 hours. *Two failures.* *Four relapses.*	11 cases: Clinical cure in 3 hours to 100 hours. Average: 46 hours. No failures. No relapses.	5 cases: Clinical cure in 30 hours to 60 hours. Average: 41 hours. No failures. *Two relapses.*
SEVERE		
6 cases: Clinical cure in 4 hours to 16½ hours. Average: 11 hours. No failures. *One relapse.*	6 cases: Clinical cure in 36 hours to 40 hours. Average (of 5 cases): 37 hours. *One failure.* No relapses.	5 cases: Clinical cure in 4 hours to 34 hours. Average: 16 hours. No failures. No relapses.

Efficacy in relation to causal organisms

Initial treatment

At 5-minute intervals. 25 cases.	At half-hour intervals. 22 cases.	At hourly intervals. 13 cases.
GONOCOCCUS		
5 cases: 1½ hours to 10½ hours. Average (of 4 cases): 7½ hours. *One failure.* No relapses.	5 cases: 24 hours to 40 hours. Average (of 4 cases*): 35 hours. No failures. No relapses.	4 cases: 4 hours to 34 hours. Average: 21 hours. No failures. No relapses.
STAPH. AUREUS		
8 cases: 5¾ hours to 22 hours. Average: 10½ hours. No failures. *Three relapses.*	5 cases: 3 hours to 60 hours. Average: 20 hours. No failures. No relapses.	1 case: 4 hours. No failure. No relapse.
STAPH. ALBUS		
—	4 cases: 27 hours to 43 hours. Average: 37 hours. No failures. No relapses.	—

At 5-minute intervals. 25 cases.	At half-hour intervals. 22 cases.	At hourly intervals. 13 cases.
DIPHTHEROIDS		
3 cases: 3 hours 3½ hours (in 2 cases).	4 cases: 50 hours to 100 hours. Average (of 3 cases): 83 hours.	1 case: 56 hours.
One failure.	*One failure.*	No failure.
One relapse.	No relapse.	No relapse.
HAEMOLYTIC STREPTOCOCCUS		
1 case: 25 minutes. No failure. No relapse.	—	—
GRAM-NEGATIVE DIPLOCOCCI		
1 case: 33 hours. No failure. *Relapse.*	—	—
FRIEDLAENDER'S BACILLUS		
1 case: 16 hours. No failure. No relapse.	—	—
MORAX-AXENFELD BACILLUS		
1 case: 16 hours. No failure. No relapse.	—	—
GRAM-POSITIVE COCCI		
—	—	1 case: 18 hours. Average: — No failure. No relapse.
NO ORGANISMS NOR INCLUSION BODIES		
1 case: 13½ hours. No failure. No relapse.	2 cases: 12 hours and 70 hours respectively.	4 cases: 48 hours to 60 hours. Average: 57 hours. No failures. *One relapse.*
VIRUS PRESUMED FROM PRESENCE OF INCLUSION BODIES		
4 cases: 3 hours to 38 hours. Average: 16 hours. No failures. No relapses.	2 cases: 78 hours and 100 respectively. Average: 89 hours. No failures. No relapses.	2 cases: 30 and 38 hours respectively. Average: — No failure. *One relapse.*

* One case is excluded as a corneal ulcer, present on admission, delayed a return to normal.

In this total of 60 cases there were therefore 1 failure in a series of 14 cases showing the gonococcus and 2 failures in a series of 8 cases showing diphtheroids; there were no failures in the 14 cases due to staph. aureus and in the 4 showing staph. albus, while the single cases due to str. haemolyticus, Friedlander's bacillus, Morax-Axenfeld bacillus, Gram-negative diplococci, and Gram-positive cocci all responded. It would therefore seem that all the common causal organisms of ophthalmia neonatorum respond to

penicillin therapy; no real significance can be attached to the 3 failures (1 gonococcus and 2 diphtheroids) in view of the satisfactory response in other (and more) cases of this type. It is also noteworthy that no failures were seen in the 7 cases in which no organism or inclusion bodies were present and in the 8 cases in which a virus appeared to be the responsible agent, judging by the presence of epithelial inclusion bodies.

At this stage it is unwarranted to draw any conclusions as to greater susceptibility of the different varieties of ophthalmia neonatorum to penicillin, but it is clear that neither the occasional failures nor relapses are explicable in terms of bacterial morphology.

A fuller account of these findings is given elsewhere (Sorsby, 1945, Sorsby and Hoffa, 1945).

2. *Penicillin in 14 cases of Blepharitis.*—In blepharitis penicillin in a concentration of 1,000 units per c.c. was used as a paint to the lid margins, after they had been cleansed by a solution of 10 vols. of hydrogen peroxide and the lid margins subsequently bathed in lukewarm water to remove all trace of the peroxide. Nine of these cases were mild and responded readily, giving a normal appearance within 3—8 days; three cases were more severe but responded as readily; of the remaining 2 cases one was unilateral and associated with considerable chronic conjunctivitis and maderosis. This latter case is greatly improved—both as regards the lid margin and the conjunctivitis—but not cured after 6 weeks' treatment; the other severe case showed no conjunctivitis but heavy scale formation at the lid margins; it was clear within 14 days.

No bacteriological tests were carried out in this series as a whole, but it may be assumed that the staphylococcus aureus was the exciting organism, a supposition proved in the severe unilateral case with associated conjunctivitis.

No adequately controlled comparison with the results obtained by the use of liquor tinctorium in blepharitis has been made, but it is clear that penicillin is not inferior to liquor tinctorium.

3. *Penicillin in 3 cases of trachoma.*—Only one of these was a fresh case:—Bridget G. aged 13 years. A typical case of trachoma with follicles at the fornices and trachomatous pannus with severe corneal involvement. The child had been treated elsewhere on and off for 18 months for chronic conjunctivitis. Inclusion bodies were present in epithelial scrapings.

Apart from atropine and an initial expression the treatment consisted exclusively of once daily paintings of the tarsal conjunctiva with penicillin in a concentration of 2,500 units per c.c. This was continued for 4 weeks, but there was marked improvement within 4 days. By the end of 12 days' treatment the typical picture of trachoma had disappeared; the pannus was minimal

and only observable with the slit-lamp. By the end of a month there was no basis for any diagnosis of trachoma. For a further month gelatine lamellae containing 200 units each were instilled nightly. Apart from roughness of the upper fornices the eyes were now normal. No further treatment has been given and the child remained under observation; the fornices assumed a normal appearance within a further 8 weeks.

A second case represented a mild relapse of a trachoma previously treated by another surgeon by the classical methods. No definite diagnosis of trachoma could be established, but all conjunctival abnormality had disappeared within a week by daily paintings with penicillin in a concentration of 2,500 units per c.c.

The remaining case, still under treatment, is a patient with long-standing trachoma. He has had bilateral tarsectomy done (Mr. Savin). Subconjunctival injections of 1,250 units of penicillin twice weekly for 2 weeks together with daily paintings of the tarsal conjunctiva by penicillin (2,500 units per c.c.) have given only indefinite results.

4. *Penicillin in interstitial keratitis.*—Three cases have been treated:—(1) an old-standing case in a girl aged 18 years. This had been treated extensively during the past 10 years by the classical methods, including injections of arsphenamides and tellurium. Her corneae are grossly scarred and her Wassermann reaction was never negative. She was admitted for intensive intramuscular penicillin therapy as there was some ciliary irritation. She received sixty 3 hourly doses of 666 units of penicillin per kilo bodyweight, the actual dosage being 34,500 units per injection and 2,070,000 for the whole course. There was only doubtful improvement in the eye condition, but the quantitative Wassermann reaction dropped from 196 to 24.

(2) A girl aged 14 years. She too had previously been treated. There was considerable activity in the left eye, the right being quiescent. Subconjunctival injection of 500 units alternate days for 10 days did not appear to influence the condition, but within a fortnight there was considerable quietening.

(3) A boy aged 6 years with a clinical history and condition as that in the previous case. A course of 60 intramuscular injections of penicillin 666 units per kilo bodyweight was given, the total being 750,000 units. There was considerable whitening of the eye noticeable as early as the 5th day of the course, but no obvious clearing of the corneal opacity of either eye by the end of the course.

Discussion

Little need be said as regards the tolerance of penicillin administered intramuscularly; the remarkably low toxicity of the drug has enabled general dosage to be elaborated with reference to

efficacy only, and not efficacy and toxicity as with most other drugs. The marked difference in the sensitivity of different organisims to penicillin has raised the question whether a standard dosage can be laid down for clinical guidance. It would almost seem as if dosage would have to be determined by the causal organism rather than by the patient's tolerance. These and other questions in relation to the general administration of penicillin fall outside the scope of the present study. They are fully discussed in the literature on the subject.

Of more direct importance to ophthalmology are the studies on the local tolerance of the drug. It may be taken as established that high concentrations of penicillin (or rather of the penicillin now available) are not without deleterious effects on the cornea, and do moreover produce conjunctival irritation. A solution containing a concentration of 2,500 units per c.c. seems to be a safe, and in most cases an adequate, application in the form of drops. Considerable clarification is still needed as to the use of penicillin in ointment form, and in lamellae. More experience is also needed as regards the tolerance of the anterior chamber to direct injection. For the present it seems that an injection of 200 units in 0·25 c.c. is as much as is justifiable to give. Injections into the vitreous clearly require considerable care, and, at the present rate, should be practised with extreme care. It is doubtful whether it is justifiable to inject more than 100 units, or even as much. There seems to be a considerable field for the use of subconjunctival injections of penicillin, for there is fairly good tolerance to daily injection of 500 units in ½ c.c. of water.

The use of penicillin locally is a matter of special importance in ophthalmology, not merely because it avoids more elaborate methods needed in general administration, but more significantly for the lack of evidence that any penicillin injected intramuscularly reaches the interior of the eye. The blood aqueous barrier does not, of course, prevent penicillin from reaching the conjunctiva and sclera, but these are tissues that are readily amenable to local treatment. The outstanding problem in the use of penicillin for intra-ocular infection is to get an adequate concentration of the drug into the interior of the eye. The various procedures that have been suggested, such as corneal bath, ionisation, subconjunctival injection, injection into the anterior chamber and into the vitreous, all have special difficulties and disadvantages. Pending further clarification subconjunctival injections seem to be the method of choice, though experimental evidence does not indicate that this is a particularly satisfactory method for obtaining any adequate concentration in the interior of the eye. It is unfortunate that so little is known of the surface tension and permeability of the cornea, for with fuller knowledge of these two physical states, the possibility of obtaining adequate concentration in the interior of the eye from the local application of drops might emerge.

In discussing tolerance and level of concentration it is of some importance to bear in mind that the normal eye of the experimental animal, and the infected eye seen in clinical practice, are not quite the same thing. There is some evidence that the impermeability of the eye to penicillin administered systemically is not so definite in the infected eye as in the healthy eye. Moreover, such intolerance as the eye shows to the injection of penicillin directly may be of subsidiary importance in comparison with the overcoming of a gross infection. Though experiments on the normal eye would indicate that intravitreal injection has to be practised with extreme caution, such treatment may be justifiable when dealing with a grossly infected vitreous. Likewise clinical results from the use of intramuscular penicillin in acute iritis and suppurative endophthalmitis are of greater significance in a final assessment than the failure to obtain any tangible concentration of penicillin in the aqueous of the normal eye of the experimental animal subjected to intramuscular injections. Studies on the infected animal eye are as yet few.

There is, as yet, no valid experimental evidence that local penicillin therapy is effective in infections of the outer eye, for the work of Robson and Scott is based on an unsatisfactory experimental lesion. The same criticism probably applies to the report by Leopold, Holmes and La Motte, who worked with a bacillus allied to the Friedlander bacillus. Until there is available an experimental lesion of the cornea that does not heal spontaneously, such studies are of limited significance. The evidence that penicillin, applied by a corneal bath and by ionisation, is effective against infection of the anterior chamber (v. Sallmann and co-workers) is more convincing. Intravitreal injection of penicillin into the experimentally infected vitreous appears to have given satisfactory results, and it is significant that the results from general administration were disappointing (Leopold). In contrast to all this uncertainty there is adequate clinical experience as to the efficacy of penicillin in the external infections of the eye. These results concern the local application of penicillin, and it is clear that both concentration and frequency of application are essential factors. This is most strikingly brought out in ophthalmia neonatorum, where concentrations of less than 2,500 units per c.c. were not found satisfactory, while the best results are obtained when drops of that concentration are put in at such frequent intervals as five minutes. In less severe infections, such as blepharitis, paints containing 1,000 units per c.c., or even less, are adequate. But it must also be borne in mind that blepharitis is generally due to staphylococcus aureus, an organism which is particularly susceptible to penicillin. Except where there is a clear indication for the use of weaker solutions, it appears that nothing is to be gained by using drops in a concentration of less

than 2,500 per c.c. for the purulent or muco-purulent infections of the outer eye. The good results obtained by Juler and Young by the use of solid penicillin crystals in infected corneal ulcers, indicate once more the need of adequate concentration, and furthermore emphasise the uncertainty of knowledge as to the limits of tolerance of the infected eye to high concentrations of penicillin.

Pending further experience it would seem that the systemic administration of penicillin has limited value. In this respect penicillin forms a striking contrast to the sulphonamides.

The sulphonamides readily penetrate the interior of the eye, and unless means are found to influence the blood aqueous barrier, or penicillin derivatives are evolved which pass this barrier, it would seem that little can be expected from systemically administered penicillin in acute intra-ocular infections of the eye. The field of action for penicillin, would, therefore, seem to be limited for the present in the external infections and here local applications, again in contrast to the sulphonamides, are highly effective.

It is, however, well to bear in mind that the relatively poor results obtained by the sulphonamides in the acute inflammations of the interior of the eye have raised forcibly the question of the nature of these inflammations. It is not at all sure that they are infections in the classical sense, and if indeed they are not, then little is to be expected from such developments in penicillin technique by which penicillin could reach the interior of the eye.

For the present penicillin has its widest application in those infections which have responded to general sulphonamide therapy, *i.e.*, essentially the external infections of the eye. It bids fair to replace the sulphonamides in this limited field, and there seems to be no reason why it should not be used systemically in such cases. Penicillin also holds out the hope of controlling early purulent infections of the interior of the eye, but again by the local application rather than stystemic injection of the drug.

The outstanding non-purulent infection of the outer eye is trachoma. Here local sulphonamide therapy has proved invaluable, possibly because the sulphonamides are not inactivated, for there is no pus. It is generally assumed that penicillin is ineffective against virus infections. Whether this also applies to the large size virus of trachoma is not clear. Experimental proof is difficult and clinical experience is as yet too limited.

The use of penicillin in syphilitic infections of the eye would appear to be theoreticaly possible. Here too difficulties arise. In the first place the blood aqueous barrier is as likely to negative the use of penicillin in ocular syphilis as it appears to negative its use in syphilis of the central nervous system. Secondly there is little evidence that such a typical syphilitic lesion of the eye as interstitial keratitis is spirochaetal in origin. If, as is generally

believed, interstitial keratitis is an anaphylactic reaction, the rationale for treatment by penicillin is not quite obvious.

The full exploitation of penicillin—as indeed of the sulphonamides—must await a fuller understanding of both the mechanism of the blood aqueous barrier and the nature of intra-ocular inflammation.

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SOME OCULAR COMPLICATIONS OF SCRUB TYPHUS*

BY

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S.E.A.C.

THE spread of the war to tropical regions has directed attention to certain diseases. One of these is scrub typhus, and as many ophthalmologists in England are probably unfamiliar with the disease a short account of it is given, and mention is made of some of the ocular conditions I have found associated with it.

Scrub typhus (Tsutsugamushi Disease) is one of the large and numerous groups of typhus fevers, which also includes the epidemic louse-borne typhus of Eastern Europe.

The causal organism is a rickettsia, the rickettsia orienta which is believed to be transmitted to man by the larvae of a mite of the genus Trombiculae. The disease is endemic in rodents in the countries of Eastern Asia, and larval mites infesting such rodents become infected. In the adult stage the mite is vegetative in habits and so is not capable of transmitting the disease. However, the infection is passed hereditarily to the next generation of larvae, which may convey rickettsia to further rodents or man.

In South-East Asia such larval mites abound in many localised areas of scrub jungle. Men, while walking, crawling or lying in such areas are liable to be infected, since the larval mite attaches itself to the skin, burrows into the superficial layers, and so passes the rickettsia into the body.

Clinical features.—There is an incubation period of about twelve days. The site of entry may be marked by an eschar; and fever, severe toxaemia, headache and prostration ensue. In some, the patients become unconscious, in others mentally disoriented. Diffuse glandular enlargement and a maculo-papular rash are common. The severity of the disease varies in different regions; the mortality rate being 10 per cent. to 15 per cent. in most outbreaks. The diagnosis is assisted by the Weil-Felix reaction, which becomes positive about the tenth day of the illness. In this reaction the serum of an infected patient agglutinates an "O" suspension of Proteus XX.

General pathology.—Together with the severe toxaemia already referred to, the essential pathological change is a generalised vasculitis affecting the arterioles and smaller vessels. This results in necrosis and destruction of the vessel walls, with extravasation of blood into surrounding tissues, and vascular blockage either by thrombosis or cellular infiltrations. These are composed of proliferated vascular endothelium and small irregular cuffs of histiocytes and plasma cells. The lesions are patchily distributed

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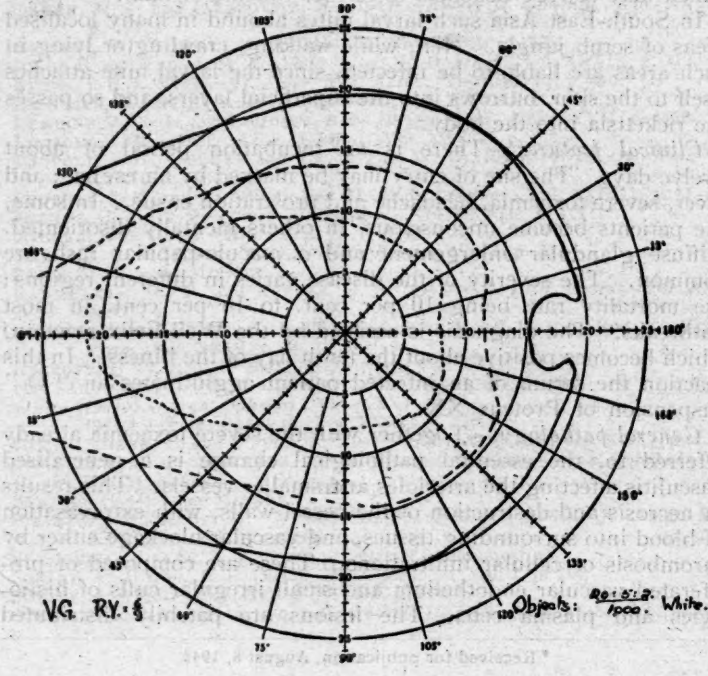
throughout all organs and the central nervous system. Generalised congestion of the brain and meninges is commonly seen at post-mortem, together with haemorrhages and vascular changes.

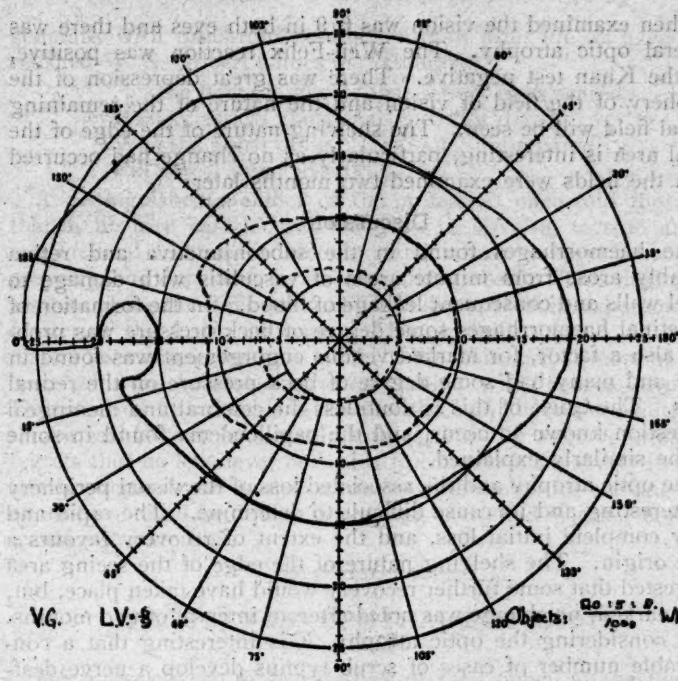
Some ocular complications.—The conditions of severe toxaemia and generalised vasculitis gives rise to certain ocular changes, some due to the toxaemia, others to areas of vasculitis occurring in the eye or visual pathway. Seventy cases which occurred in Assam were examined, and notes are given of those showing ocular changes. The Weil-Felix test was positive in all, except one who died too early in the disease for the test to be significant.

Congestion of the conjunctiva occurs invariably in the acute phase of the disease, so constantly that it is a clinical feature rather than a complication of the disease.

Subjunctival haemorrhages were seen in four cases. They are usually of small extent but one case showed extensive bilateral haemorrhages. It is interesting to note that similar haemorrhages are met with in malaria, a point to be kept in mind in diagnosis, since both diseases occur in similar regions.

Marked engorgement of the retinal veins was noted in seven cases. This probably represents an under-estimate of the frequency with which some degree of engorgement is present, as only marked changes in calibre were considered.





Papilloedema was present in four cases and was bilateral in all except one. In three of them there was increase of intracranial pressure and this was associated with increase in the protein content, and cells were increased to 60 or so per c.mm.

Retinal haemorrhages occurred in four cases, two of whom also had papilloedema. They were usually small, few in number and in the nerve fibre layer, being situated in the region immediately surrounding the optic disc. One case, however, showed numerous haemorrhages which encircled the discs on both sides.

One interesting case of bilateral optic atrophy was seen six months after the acute stage of the illness; and a summary of the case and the central field charts are given.

Case of L./Cpl. V. G., aged 30 years

The patient was acutely ill for two weeks, and one week later noticed a defect in the vision of both eyes. After three days he could only see hand movements close up to the face, and this visual state remained unchanged for six weeks. Thereafter vision commenced to improve, and at the time of examination he could see quite well straight ahead, but had difficulty in seeing at the sides and at night. No quinine or arsenicals had been given.

When examined the vision was 6/9 in both eyes and there was bilateral optic atrophy. The Weil-Felix reaction was positive, and the Khan test negative. There was great depression of the periphery of the field of vision and the nature of the remaining central field will be seen. The shelving nature of the edge of the visual area is interesting, particularly as no change had occurred when the fields were examined two months later.

Discussion

The haemorrhages found in the subconjunctiva and retina probably arose from minute areas of vasculitis with damage to vessel walls and consequent leakage of blood. In the formation of the retinal haemorrhages some degree of back pressure was probably also a factor, for marked venous engorgement was found in some and many had some degree of back pressure on the retinal veins. The cause of this is doubtless the cerebral and meningeal congestion known to occur, and the papilloedema found in some can be similarly explained.

The optic atrophy and the associated loss of the visual periphery is interesting and its cause difficult to determine. The rapid and fairly complete initial loss, and the extent of recovery favours a toxic origin. The shelving nature of the edge of the seeing area suggested that some further recovery would have taken place, but, as remarked, no change was noted after an interval of two months.

In considering the optic atrophy, it is interesting that a considerable number of cases of scrub typhus develop a nerve deafness. It is odd that this nerve should be singled out, and, as in the case of the optic nerve, the cause may be a toxic one.

I have pleasure in thanking Major M. T. Parker, R.A.M.C., for his help in the pathological aspects of this disease, and make acknowledgment to the appropriate Army authorities for permission to publish these notes.

ANNOTATION

Word blindness

The paper published in our last issue on word blindness is of great interest, and the suggestions as to teaching a backward child to read most valuable. All of us must have met with similar cases either at school or in after life. It is of course conceivable that the school boy, who dreads being put on to construe in class, may not have prepared his lesson beforehand, either through sheer laziness or from having been employed in some other more interesting occupation. In our own school days we were something of an authority on *ex tempore* improvisation in translating a Latin sentence,

generally with disastrous results. And in after life we have often relished W. S. Gilbert's lines in "Haunted."

> . . . the horrible ghosts that school days scared:
> If the classical ghost that BRUTUS dared
> Was the ghost of his "CAESAR" unprepared,
> I'm sure I pity "BRUTUS."

A distinguished member of the profession once told the writer that in his own case he was very slow in learning to read and he was inclined to blame a ductless gland which was not functioning properly, and only took up its work after puberty. This might have accounted for the difficulties which William Dobbin experienced in mastering the Latin grammar. Though dull at Latin, at mathematics he was uncommonly quick. We believe that most of these cases of word blindness have no trouble with figures. Anyhow Dobbin lived to write his History of the Punjab, and the author of the paper has overcome his difficulties; but the writer of this note regrets that he has never been able to conquer his inability to translate a simple Latin sentence, or his propensity for making false quantities. And he doubts if a course of thyroid or other hormone would ever cure him.

FACULTY OF OPHTHALMOLOGISTS

Meetings between representatives of the Council of the Faculty, the Council of the Association of British Ophthalmologists and the Council of the Ophthalmic Group Committee (British Medical Association) have been held. Agreement has been reached regarding the constitution of the Faculty, including new criteria for membership and associateship, and revised arrangements for the election of Council. For the original statement on the formation of the Faculty, reference should be made to the *British Journal of Ophthalmology* of February, 1945, to the *British Medical Journal* of February 3, 1945, or to the *Lancet* of February 3, 1945. As a result of this agreement the Council of the Association of British Ophthalmologists were enabled to urge all their members to join the Faculty and to approve the dissolution of the Association in order that it may be merged into the Faculty. A postal ballot of members of the Association has revealed the necessary majority in favour of dissolution. A new Council of the Faculty is to be elected after due time has been allowed for all, includine serving ophthalmologists, to join the Faculty; in the meantime any applications for membership or associateship which present any doubt are to be scrutinised by a joint Committee representing the Council of the Association of British Ophthalmologists and the present Council of the Faculty.

The following are the new criteria:—

Membership

1. Any ophthalmologist of the status of ophthalmic surgeon or assistant ophthalmic surgeon, who holds an appointment on the staff of a voluntary or municipal hospital with a recognised Eye Department.

2. Any ophthalmologist, no longer on the active staff of a Hospital, who has held such an appointment.

3. Other ophthalmologists of consultant rank approved by the Council, including those in the Services or holding Government appointments, and those of the British Commonwealth and Empire overseas.

Associateship

1. Full-time ophthalmologists of two years standing.

2. Part-time ophthalmologists of two years standing, holding a Hospital appointment or possessing a special diploma.

3. Practitioners who on June 1, 1945, were on the N.O.T.B. list.

Council

The Council shall be increased in number to 25; the number of regions to be increased to 6, to correspond with the regions defined by the British Medical Association.

The Council shall be constituted as follows:—

1. One member shall be elected from each region by a local regional vote of members.

2. Twelve members shall be elected by a national vote of members.

3. One associate shall be elected from each region by a local regional vote of full-time associates, representing the full-time associates.

4. One part-time associate shall be elected by a national vote of part-time associates, representing part-time associates.

5. Any member of Council shall be free to stand for election indefinitely if properly proposed and seconded.

The outline of the Constitution, functions and management of the Faculty included in the statement published in the medical press and as amended above will in general terms remain valid. As soon as the new Council is elected, the Constitution and Bye-Laws will be legally drawn up.

Forms of application for membership or associateship of the Faculty may be obtained from the Honorary Secretary, 45, Lincoln's Inn Fields, London, W.C.2.

STEWART DUKE-ELDER, *President*,
FRANK W. LAW, *Secretary, Faculty of Ophthalmologists.*

J. N. TENNANT, *President*,
H. R. BICKERTON, *Secretary, Association of British Ophthalmologists.*

ABSTRACTS

MEDICAL OPHTHALMOLOGY

(1) **Mann, Ida (Oxford).—Ariboflavinosis.** *Amer. Jl. Ophthal.*, Vol. XXVIII, p. 243, 1945.

(1) **Ida Mann** discusses the clinical appearances of ariboflavinosis in the eyes, and describes a case of this disease. The earliest sign is budding of new capillaries from the apices of the limbal vascular loops with extension on to the cornea. There are generally three arcades of new vessels, and both eyes are affected around the whole circumference of the cornea. The depth of the vascularized area varies in the two eyes. The diagnosis is verified therapeutically by the emptying of the new vascular loops after the administration of riboflavine.

In the case described in this paper there were also concentric opacities in the cornea beyond the arches of the new vessels. Some of the new vessels passed deeply into the substantia propria in the neighbourhood of these corneal opacities. The cure was dramatic, for with the administration of riboflavine, 15 mg. a day, there was rapid emptying of the vessels, and a cure in four days. One eye received local treatment, including atropine, but the other eye which had none, did as well or better than the former.

H. B. STALLARD.

(2) **Stephenson, W. V. (Toledo, Ohio).—Anterior megalophthalmos and arachnodactyly.** *Amer. Jl. Ophthal.*, Vol. XXVIII, p. 315, 1945.

(2) **Stephenson** describes the case of a white female, in whom the signs of arachnodactyly were evident at the age of five months. The cornea measured 15 mm. in the horizontal meridian, and 14·5 mm. in the vertical. The right pupil was displaced nasally and upwards. The pupils were pear-shaped and the irides atrophic.

The skull was dolichocephalic, the chest funnel-shaped, the long bones abnormally long and thin, and the hands and feet likewise. There was muscular wastage of the arms, forearms, hands, thighs, legs and feet. A tiny supernumerary digit was present on the ulnar side of one hand.

H. B. STALLARD.

(3) **Laird, R. G. (Grand Rapids, Michigan).—Iodide therapy for senile macular degeneration.** *Amer. Jl. Ophthal.*, Vol. XXVIII, p. 287, 1945.

(3) **Laird** discusses the pathology of senile macular degeneration and describes the results of treatment by iodides in a series of 67

patients with a total of 115 eyes. Protiodide of mercury gr. 0·125 to gr. 0·25 was given orally thrice daily. When this failed to maintain visual improvement, subcutaneous injection of iodides was given. Fifty-six eyes improved with oral administration. Ten eyes showed no change with oral administration, but improved when iodides were injected subcutaneously. The average improvement of the 115 eyes was 89 per cent.

H. B. STALLARD.

(4) **Harley, R. D. (Canal Zone, Panama).—Kerato-conjunctivitis caused by the dranzanillo tree.** *Amer. Jl. Ophthal.*, Vol. XXVII, p. 628, 1944.

(4) **Harley** describes the clinical features of the toxic effect of the sap of *hippomane mancinella L* (beach apple) on the eyes and skin. An irritating milky latex is exuded by broken leaves and branches, and a heavy dew may extract the sap which falls upon anyone lying beneath the tree.

The eye changes consist of a severe kerato-conjunctivitis, blepharospasm, coming on within a few minutes to an hour after contact, and considerable pain. The cornea and conjunctiva are denuded of epithelium, and fluorescein staining persists for 5 to 7 days. The lids are oedematous and vesicles are present.

The skin changes are those of dermatitis venenata, the face, arms and trunk being chiefly affected.

The author recommends bathing in sea water with the eyes open as a first-aid measure followed by a thorough cleansing with soap and water. Copious irrigations of the conjunctival sac with normal saline, pantocain drops or ointment 0·5 per cent. and cold boric acid compresses are given. The skin is treated with cold compresses and calamine lotion.

H. B. STALLARD.

(5) **Thomas, C. I. (Cleveland, Ohio).—Suction instrument for cataract extraction.** *Amer. Jl. Ophthal.*, Vol. XXVIII, p. 317, 1945.

(5) **Thomas** describes a simple suction instrument for cataract extraction. It is composed of Dimitry's syringe connected by an adaptor with 6 inch of firm rubber tubing. The suction cup is attached to the other end and it corresponds in curvature to the Kirby intra-capsular forceps.

The instrument displaced a 5 mm. column of water 45 mm. in height. This was increased to 65 mm. by shortening the stem of the piston.

H. B. STALLARD.

CORRESPONDENCE

USE OF A FINE METAL RING IN THE LOCALISATION OF INTRA-OCULAR FOREIGN BODIES

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—In the article by H. B. Stallard in the Journal for March, 1944, referred to in a letter by L. B. Somerville-Large in the current number a description is given of the use of a fine limbal metal ring and of a method of taking the X-ray photographs.

The purpose of this letter is to state that fixation of the head, the use of a fine metal limbal ring and the method of taking the X-ray photographs described were in routine use in the Sunderland and Durham County Eye Infirmary in 1915. The originator was Alfred Clarence Norman, M.D.(Edin.), who was then House-Surgeon and is now Professor of Radiology in Baghdad.

Yours faithfully,

JAMES A. ROSS.

SCONE PALACE, PERTH,
September 9, 1945.

OBITUARY

SIR JAMES BARRETT

ON April, 6 1945, the dynamic and gifted personality of James William Barrett, K.B.E., passed on. It is fitting now for us to ask, What works he performed and what was the source of his enthusiasm? That he performed works and possessed enthusiasm beyond the average man is undoubted. Humorously it is told of a visitor to Melbourne who, finding the city unduly crowded and asking the cause was told, "The secretary of Sir James, by mistake has called all his commlttees together on the same day."

Much of interest and not a little inspiration can be drawn from a consideration of his long and useful career. What were the gifts, physical and spiritual that enabled him to do what he did? What was it that lit the fire in his early youth and impelled him "to seek, to strive, to find and not to yield?" Was it his Quaker ancestry, or was it the youth of his native land that fired him? Melbourne had been a city but for twenty-eight years when he was born! In many ways it can be seen that ideas for the betterment of his fellows and of his native land were absorbed early, and they

laid the foundation for a life-time of selfless devotion. We can recall his love of Australia's fauna, for example, the papers he wrote concerning their anatomical mysteries, their incalculable value and the urgent need for their preservation. We remember his own Zoo at his home. He attributed this interest to the enthusiasm of his school-day teacher and friends, Alexander and William Sutherland. From this arose also his interest in national parks.

To unusual physique and remarkable mental powers must be added an ability to become infected by the best that was in the minds of his associates. Once he was infected his aim was at the highest, regardless of personal cost and the passing of time. No mere visionary or theorist however was J.W.B. He was practical and concerned with " A Vision of the Possible."

One, in a position to judge, wrote: " No man in Australia shouldered more responsibility in cultural, humanitarian and social movements than this wise and far-sighted organiser, who laboured for love of service beyond any thought of reward."

At the time of his death he was actively interested in no fewer than 28 Committees, of which he was President of 11, Vice-President of two, Chairman of seven and Honorary Secretary of three. One had to know him and to see him at work to realise what being " actively interested " meant to him. He was always alert, his facts always appeared to be ready and mobilised and based on his years of experience, he would give advice of unusual wisdom. He had a fine presence and as Sir Henry Newland wrote, " a voice in keeping with his physique, associated with an oracular manner of delivering his quasi-delphic utterances. One can imagine a man being expert in two or three subjects, but here was a man who had at his busy finger-tips the manifold interests to which he was devoted. " These ranged from Music to Educational Reform; Parks and Playgrounds to Proportional Representation; Bush Nursing to Magna Carta; Town Planning to Decimal Coinage; Calendar Reform to the Royal Empire Society; Social Diseases to Life Saving; Radio to Neglected Children; Historical Monuments to Native Fauna, and Repatriation to the Welfare of Soldiers' Children." His honours and degrees included K.B.E., C.B., C.M.G., M.D., M.S., F.R.C.S., F.R.A.C.S., LL.D., C.M.Z.S.

We could, if space permitted, concentrate on him as a seeker after truth, a preventer of disease, a pioneer of social reform, a lover of nature and of music, or as an imperialist. A general survey however is indicated.

His four-score years.—What a span of life was his, passing from a year when Bismarck became Chief Minister and the American Civil War commenced and the " Shenandoah " failed to enlist recruits in Melbourne, till the first stage of the second

world war was brought to its end. He could recollect the landing of Queen Victoria's wayward son, the Duke of Edinburgh at Sandridge, which is now Port Melbourne, and the toll gates across St. Kilda Road. Seventy years later he, as Chancellor of the University, conferred an honorary degree upon Queen Victoria's great grandson, the Duke of Gloucester, now Governor-General of Australia.

In his memoirs, posthumously published, he recalled the Psalmist's lament, "My wounds stink and are corrupt." When he was a final year student all abdominal perforations, whether accidental or operative, ended fatally. The surgeons in those days operated in old blood-stained coats and often held their instruments in their mouths. Injured persons refused to go to hospitals. A new era opened when one of Lister's house surgeons passed through Melbourne. The antiseptic method that Bismarck tried to outlaw as criminal has saved many lives. J.W.B., remembering all this, lived to treat ocular infections with penicillin and the sulphonamides.

The Barrett's were probably of Norman extraction, and the pioneer was possibly one of William the Conqueror's knights. The shield of arms was given for services in the Levant in the fourteenth century when the family lived in Wiltshire. His father was Dr. James Barrett, J.P. He was born in Banbury, and obtained his medical diplomas in London. In 1859 he took medical charge of an emigrant ship to Melbourne, and while waiting for a return passage was appointed resident medical officer to what is now the Women's Hospital. He was characterised by great energy and physical strength. How the medical outlook changed! When a young apprentice, the death of a patient from septicaemia following a dog's bite was classed as a visitation by God for earlier misdeeds! He became a physician to the Alfred Hospital in 1870.

His mother was born in Bridgnorth, Shropshire. He was the eldest of nine children, his mother dying when he was but twelve. After being at the Church of England Grammar School, he was sent to Carlton College of which he became *dux* at the age of fourteen.

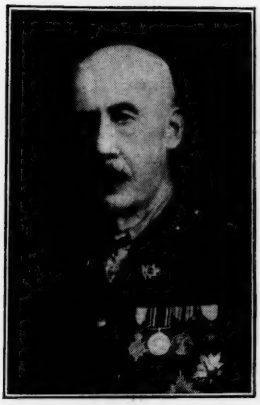
His association with the University is unique and redounds to his credit. He entered it on his fifteenth birthday when it had 200 students. He saw it grow to 4,500. He matriculated in February, 1877, and at the end of that year completed his first year with first-class honours and the exhibition. His results were similar next year. In his third year George Adlington Syme shared the exhibition. In the final year Syme came first and Barrett second amongst the nine graduates. The examination for M.D. was passed in February, 1887; and for M.S. in February, 1888, the other candidate being Syme. He became Vice-Chancellor in

1931, succeeding the late General Sir John Monash. Four years later he succeeded the late Sir John Macfarland as Chancellor, and continued in that office until 1939. For 44 years except for his absence on war-service he attended Council meetings.

His connection with the Faculty of Medicine was set out in a minute from which the following are extracts: "Throughout the long period of his membership of the Faculty he took an active and untiring interest in its affairs and made a sustained contribution to the cause of medical education in this State. . . . The University records show that he acted as demonstrator in Physiology in 1887 and 1898. He became Assistant Lecturer in Physiology in 1899, and from 1903 to 1935 was Honorary Lecturer in the Physiology of the Special Senses. He resigned this position on becoming Chancellor of the University in 1935. Although he identified himself with many phases of the University activity, the Faculty of Medicine was probably the body in the University to which he was most firmly attached, and the Faculty's sense of the heavy loss which the University has suffered in his death is therefore peculiarly great."

Sir James was a member of the University Council from 1901 until his death. He took a very active interest in all University affairs, especially with regard to University Extension and musical developments. He was Chairman of the Conservatorium Finance Committee and of the Melbourne Symphony Orchestra Executive Committee at the time of his death. He had a genuine love of orchestral music, fostered by a deep friendship with the first Ormond Professor, Marshall Hall. To Sir James was due the shrewd, business-like direction of the Lady Northcote Permanent Orchestra Trust Fund and the Sidney Meyer Free Concert Trust. "One abiding memory of a holiday since his eighty-third birthday was of the veteran sitting down to the piano at a seaside guesthouse and entertaining the company with Gilbert and Sullivan, complete with running annotation." In the early days J.W.B. scoured the city to find woodwind and brass players who were competent. At his memorial concert in 1945, the conductor, his brother-in-law, Professor Bernard Heinze, said, "We dedicate this Sidney Meyer concert to the memory of Sir James Barrett. To him music was no mere life-long interest; it was part of his very being. He gave himself unselfishly to the cause of all aspects of musical activity in the community and, happily, he lived to see some of the fruits of his labours. To-day's over-crowded halls of eager music-lovers bear witness to the wisdom and faith of Sir James Barrett. Australia is infinitely the poorer for his passing, and Music here must be forever indebted to him."

First medical practice.—After almost three years in residence at the Melbourne Hospital he resigned. While at the hospital he wrote "Part 1 of A Treatise on Typhoid Fever." With a view



SIR JAMES BARRETT*

* We are greatly indebted to the Editor of the *British Medical Journal* for the loan of the block for illustration.

to recuperate his health and to prosecute further the study of his profession he went to England. Three weeks after he arrived he entered for the M.R.C.S. examination. " Out of the two thousand students who have passed through the College since its foundation, not one of them obtained an equal number of marks.

It is on record that he was the first graduate of the Melbourne University to obtain an appointment in England. J.W.B. wrote of this as follows: " Australia has won at cricket, but this is the first time we have scored at medicine." " I am now but twenty-two years of age, so that by working hard for about twenty years, I shall be able to make a name." At King's College he was Demonstrator of Physiology for two years. Professor G. F. Yeo wrote in 1886, " Great earnestness, quickness and assiduity as a worker are perhaps the most striking traits in his character, but they do not surpass the genial urbanity and unvarying courtesy which close acquaintance shows to be inseparable from his disposition." He was assistant in the Aural Department, and his work in the Pathology Department was such that Professor A. B. Duffin recognised " all the higher qualities suggestive of future eminence." His main work was done at Moorfields where he was a Clinical Assistant for two and a half years. Marcus Gunn wrote, " I cannot speak too highly of Mr. J. W. Barrett's professional acquirements; his training has been one of exceptional thoroughness. . . . As a microscopist, Mr. Barrett's contribution to the minute anatomy of the mammalian retina . . . has added greatly to our knowledge of the subject." His first papers in London appeared in the Medical Times and Gazette, 1883. They were " Two Cases of Neurofibromata " and " Hydatid Disease in Victoria." Then followed a paper on the cause of the first heart sound and the nature of the movement of the cardiac muscle. So diverse were his interests that soon afterwards the Liernur system of sewage, a new microtome, the velocity of accommodation, the use of homatropine and the mammalian retina received attention. In the next three years sixteen more papers appeared, one jointly with A. S. Morton and five with William Lang. The latter wrote of " the untiring energy, keen observations, and original views which will, at no distant future, place my friend in the foremost rank of scientific medical men."

One of his examiners was Sir William Bowman who asked J.W.B., " Why some animals have round and some slit-like pupils." Jonathan Hutchinson when examining in surgery asked him, " How kangaroo tendon was prepared for ligatures in Melbourne." During this period he studied bacteriology in Berlin under Robert Koch—who was " efficient, intolerant, and with little interest in the work being done in other countries." Morton, Waren Tay, Silcock and others wrote with regret at his departure from London.

That he fulfilled their expectations as a research worker and as a clinician will be seen by the following references. Little, however, did they realise that his interests would be so wide.

The prevention of blindness and the care of the blind.—On his return to Melbourne in 1886, J.W.B. was appointed as clinical assistant to the Eye and Ear Hospital. The other surgeons were Dr. Andrew Gray, who had been trained by Sir William Wilde, Dr. Aubrey Bowen, " a very good operator," and Dr. J. P. Ryan, who was assistant surgeon. " The work was conducted in a small imperfect building on the present site, which, with the authority of the Committee, I got enlarged. Prior to this arrangement, Dr. Gray had a clinic near the site of the present Dental Hospital. Dr. Bowen had a similar arrangement somewhere else, and it was the amalgamation of the two which resulted in the foundation of the Eye and Ear Hospital. When I returned Dr. Ryan became full surgeon and I became assistant surgeon, and Dr. Kenny was the resident. Bowen soon retired owing to health, and I became full surgeon." This is an extract from a letter from Sir James written on March 2nd, 1945. In his early days trachoma or " sandy blight " was a scourge, but, by the end of his life, an early case of this disease was a very rare finding in Victoria.

Sir James remained on the staff until 1913, when he was appointed ophthalmologist to the Melbourne Hospital.

Sir James was Honorary Oculist to the Royal Victorian Blind Institute for forty-five years. During this period he saw its activities increase four hundred per cent. He was greatly interested in the prevention of blindness and in the amelioration of the lot of the afflicted. He saw those that were an hungered, those that were sick and those that were blind, and he did what he could for them.

The Bush Nursing Association is his greatest and his noblest memorial! This he founded with the late Countess of Dudley, when Lord Dudley was Governor-General of Australia. Now it contains eighty-odd hospitals and centres, self-supporting and locally controlled. " For a membership fee of about thirty shillings a year, it gives hospital treatment to the member's family for about fifty shillings a week, equal to that which costs five times that fee in many of the Government-controlled hospitals." By restriction of its Trust Deed, this association cannot come within twenty miles of the city, but at the borderline are the " show " hospitals of the urban Melbourne—at Chelsea and Ferntree Gully. A wing at the former is dedicated to his memory.

Sir James was a lover of research. He had planned to spend his life in London carrying out original investigations. Family reasons, however, called him back to Melbourne.

His fellow oculists learned early to realise his exceptional grip of ophthalmology and of many other interests—but still their

wonder grew as they learned more of his amazing ability. What was the secret of his knowledge? How could he be always so ready to present his case so clearly? Did he have a staff of secretaries reading, translating and cross-indexing? No; but he was possessed of a clear mind, a retentive memory and methodical habits. His library was as well stocked and as well under control as his mind. In 1929 he wrote, "Every evening when I can be at home, I go over the outline of some particular activity and try to grasp its essentials. Then by means of cross-filing and indexing I arrange the details I have read, so that they are available for all-time for ready reference." Alas! that we were not all taught to do this as an essential part of our medical course.

Sir James was the author of "Twin Ideals," 1918, "The A.A.M.C. in Egypt," 1918, "War Work of the Y.M.C.A.", 1919, "A Vision of the Possible," 1919, and "Save Australia." "Eighty Eventful Years" was published posthumously, and should be read by all Australia's youth. His splendid son Keith was killed, and his father published his diary as "The Diary of an Australian Soldier" in 1920.

He joined the Ophthalmological Society of the United Kingdom in 1889. He is survived by only three or four of the early members, including Dr. A. L. Kenny of Melbourne. When a similar society was formed in Australia he naturally became the first President. His Presidential address, "Blindness, Partial Sightedness and the History of the Braille Type," dealt with a subject very dear to him. He held that the prevention of blindness should ever be uppermost in the ophthalmogist's mind. He took part in the discussions at the last meeting of this Society, and dealt with various problems with his characteristic force and lucidity.

Sir James was on the General Committee of the British Journal of Ophthalmology from its inception. His enthusiasm almost to the day of his death is shown by the publication of letters from him in each of the last copies of this Journal appearing before his death. They were entitled "Penicillin" and "Phlyctenular Disease." At the Annual Meeting of the B.M.A. in 1886 he had read a paper on "Sycosis and Phlyctenular Ophthalmia"!

J.W.B. was elected President of the B.M.A. in Victoria in 1901 and again in 1930.

In 1935 when the annual meeting of the B.M.A. was held in Australia, following the death of Sir Richard Scawell, Sir James became president, the highest honour in British medicine. At this time Lord Horder stated that Barrett "seemed to have been the pioneer in all the things that one could think of by which the human race might be bettered and improved."

It was characteristic that he volunteered in 1914 on the outbreak

of war. He left Australia in December, 1914, an Honorary Major without pay or allowances, as Registrar and Oculist to the first Australian General Hospital. His powers of organisation were shown when the casualties began to pour in from Gallipoli. The hospital accommodation at Heliopolis rapidly increased from 500 to 8,000 beds. Of the part J.W.B. played, Sir Frederick Treves when visiting Cairo said, " This is the second time in the history of Egypt that someone has made bricks without straw." In June, 1915, he became Honorary Lieutenant-Colonel with substantive rank, " for exceptional services rendered to the wounded at Helles." Soon after this he was A.D.M.S. to the A.M.F. in Egypt. He resigned his Australian commission in November, 1915, and early in 1916 was gazetted Lieutenant-Colonel in the R.A.M.C. Among the appointments that he held in Cairo on his return from sick leave in London, were member of the Council of the British Red Cross, Consulting Aurist to the Egyptian Force, and President of the Standing Medical Boards in the E.E.F., exclusive of Alexandria.

Too many tasks were thrust on him and much criticism was made of his inability to achieve the impossible. His observations on pellagra as a cause of night blindness were stimulating, and Colonel Graham Butler considered that the problems of vision in the army have never been better stated than by Sir James at this time. " As President of the Permanent Medical Board he instituted reforms which not only were of great value to the British Force in the East—they saved two divisions of infantry for the front—but set a standard which influenced military procedure." In 1916 he was awarded the Order of the Nile. He was twice mentioned in despatches, and in 1918 received the C.B. and the K.B.E. He was the first secretary of the Australian Red Cross after it was founded in the Government House Ballroom, Melbourne, in 1914.

It was a habit of mind of many Melbourne citizens to think, " Sir James can get that done," or " We will ask Barrett's advice." We marvelled at his industry and we could rely on the sagacity and the devotion to service of this amazing citizen. The passing of his four-score years scarcely lessened his mental vigour or damped the ardour with which he prepared for future developments. At his death there stood on the business paper of the University council a notice in his name bearing on its future activities. A study of his character and his methods answers the query raised by his critics' repeated comment, " Barrett got his way once again." Professor W. A. Osborne was particularly struck by his remarkable grasp and his memory of detail, his imperturbable temper in debate, particularly if voting went against him, his organizing ability and rapid mastery of confronting problems, his ability to have ready a prepared constructive

scheme, and his willingness to rely on expert's advice in their own fields.

Sir James was greatly interested in adult education. The example set by the University of Wisconsin impressed him. Its council accepted the education of the adult population in the State as its responsibility. So keen was Sir James that he paid all the expenses of the visit of Dr. Mansbridge to Australia. Similarly he, with Sir George Fairbairn, in 1913 financed the British Parliamentary Delegation that visited Australia. Sir James did much to tighten and strengthen the bonds that knit together the scattered elements of our Empire.

When he received the honorary degree of LL.D. from Manitoba University, he was described as being " Eminent as a surgeon, soldier, author, and philanthropist—a great Australian whom a sister Dominion delights to honour."

It was fitting that his funeral cortege was diverted through the University grounds. The Chancellor, Mr. Justice Lowe, referred to Sir James as one of the most distinguished citizens of his generation. " No one in the past 40 years exercised a greater influence on the work of the University than he." The Premier said that he was one of the most public-spirited citizens Victoria had ever known. In the Foreword to Sir James' last book, Sir John Latham wrote, " He has had critics and opponents, but I find no unkind word about them in this book."

He was married twice. The first Lady Barrett was a daughter of Mr. Charles Rennick. She predeceased him in 1939. His second wife was Miss Monica Heinze. She and his three daughters and one son survive him, and to them we extend our sincere sympathy.

His words concerning another apply well to him. " It is an old story, that one man, fortunately placed and possessing clear vision and high ideals, effected so much." Most of his fortunate placing was the result of his own enthusiasm and devotion to the service of mankind. So pervasive was his beneficial influence in the scientific, artistic and social life of his country that we are more indebted to him than we can say and probably more than we, as yet, realise.

Sir Herbert Eason writes:—

Sir James Barrett's academic and scientific career has been set out above, but as I lived and worked in intimate association with him for four years (1915—1919) in Egypt in the last war, it may not be inappropriate if I attempt a short sketch of him " in his habit as he lived."

Barrett was a big man both mentally and physically. He was over six feet in height and wore a beard which seemed incongruous

with any uniform. He usually wore a rather shapeless field service cap, and his uniform was not smart or well-fitting. In fact his personal appearance did not appear to be of much moment to him and he might often wear his gaiters on the wrong leg or his spurs upside down.

But one could not talk to him for an hour without realising that here was a man of great personality and brain power, quite belying that apophthegm of Bacon's that " Wise nature did never put her precious jewels into a garret four stories high; and therefore exceeding tall men had ever very empty heads." His interest in all things was intense. Politics, social problems, natural history, men and women, were all matters with which he was deeply concerned, and he had the capacity of interesting others in his own interests. He was a fluent and inspiring speaker and could attract large audiences of soldiers to his lectures in the Y.M.C.A., lectures which might deal with such diverse subjects as Town Planning, Bird life on Flinders Island, Bush Nursing Service in Australia, or almost any other topic of the day.

He was essentially a publicist. He simply *had* to let the public know his views on any subject, and his letters to the Press both in Egypt and Australia dealt with almost every aspect of social and public life. It may be apocryphal but the story goes that someone in Australia produced a dummy pamphlet with the title, " Advice to the Creator, or what to do with the Universe when I am gone, by James W. Barrett."

As a publicist he was by no means averse from stealing other people's thunder. He would hear some remark or opinion overnight which attracted his attention, and next day he would very likely address a letter to the Press on that subject.

Needless to say, such a publicist trod on many people's corns and was not always popular, but this did not affect him, for he was solely concerned with what he considered the public good. He was a good golfer, as remorselessly purposeful within his limits as he was in his acts and writings.

His sense of humour, particularly that which arises from the appreciation of one's own foibles as well as those of others, was somewhat deficient, but he was highly appreciative of humour in books, " O, Henry " being his favourite.

Taken all round, however, he was a man of commanding intellect and a colleague whose company was never stale or wearisome, and whose conversation was weighty and stimulating.

His distinguished career in Melbourne, crowned by the Chancellorship of the University, was a fitting tribute to his mental powers and public spirit.

H.L.E.

NOTES

Death

DR. ARTHUR GREEN BRINTON, of Johannesburg, ophthalmic surgeon, born July, 1875, at Edgbaston, Birmingham, passed away peacefully on July 5, 1945. He came to Johannesburg in 1902, and was one of the first specialists in the City. He was a prominent member of the medical profession, was lecturer in ophthalmology at the University of the Witwatersrand, consulting eye surgeon to the General Hospital and Dental Hospital, and Major, South African Medical Corps. He was, up to the time of his death, in active practice and was popular in wide circles, being a well known golfer and member of the Senior Golfer's League.

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University of Glasgow Department of Ophthalmology Autumn Term, 1945

DURING the autumn a series of meetings will be held in the Department on Wednesdays at 8 p.m. The general arrangements will be similar to the series held last year. Tea will be served after the paper and a discussion will follow. The meetings will be open to all medical practitioners and senior students interested jn Ophthalmology.

September 19, Prof. W. J. B. Riddell—"Synthetic Mydriatics"; September 26, Prof. A. J. Ballantyne—(i) "Small Retinal Exudates"; October 3, Prof. A. J. Ballantyne—(ii) "Massive Retinal Exudates"; October 10, Prof. A. J. Ballantyne—(iii) "Tumours and Pseudo-tumours"; October 17, Dr. I. C. Michaelson—"Ophthalmology in the New World and in the Old"; October 24, Mr. R. C. Davenport—"St. Dunstan's in the Recent War."

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Physiological Optics in the U.S.S.R.

THE Academy of Sciences of the U.S.S.R. is to be congratulated with a new and important undertaking started in 1941—a new Department of Physiological Optics. In two volumes, first one published in 1943, with a general index of papers in German contained, and the second one published in 1944, with a summary in English of everyone of the papers contained, the academy certainly put the scientific world in its debt by the richness of the material collected under the name of the problems of physiological optics. The British reader ought to be warned not to mix this name with a deplorable state of "optics" (*i.e.*, ophthalmic opticians, consulting opticians, etc.). In this country there is no powerful financial interest at the base of this Optical Institute to interfere with the proper development of ophthalmology, purely scientific and applied, and the whole movement is entirely in the hands of ophthalmic surgeons and physicists. Some of them are already well known to the international ophthalmic fraternity, like Averbach, Vaviloff, Krafkoff, Rabkin, the late Lazareff, Orbeli, the pupil and heir to Pavloff, contributes as well. Others, and their name is nearly a legion, publish the results of

their experiments, chiefly on voluntary human subjects, made under the guidance of more experienced colleagues like Fedoroff or Teploff. It is impossible in a review to describe the summary of all of them; suffice is to say, with the development of the aviation, physiological optics are becoming of tremendous practical importance. The second volume, as mentioned above, is available in its summaries to every English speaking reader. Both volumes are full of bibliography on the subjects in all European languages. Teploff measured the absolute sensitivity of the eye towards inducing light (*i.e.*, the second source of light) in the presence of the first one (the reagent). He found that the inducing light reacts negatively on the reagent one in near proximity, but positively if further away. Galochkina made similar experiments with red and green lights, and found that in the former light the inducer increases, and in the latter decreases the sensibility of the eye (in a normal person). Nothing of this kind was noticed with dichromates. Zaretzkaja found that the intra-ocular tension is lowered by the green and increased by the red light. Again the dichromates do not react this way at all. Gasofsky found that allowing light to be projected on the non-working eye when the other eye looks in a monocular apparatus (like a microscope) increases the sensitivity of the working one. Dzidichwili shows that the differential sensibility of the eye is worsened by an additional off-side source of light. Lasereff publishes special experiments to confirm that of Wood-Landua. Meskoff and Brullova show the decrease of the eyesight with the increase of brilliancy of illumination. Bogoslafsky and Kravkoff found that the noise of the aviation motor after 15 minutes produces an increase of the central, but the decrease of the peripheral vision. Kravkoff found that the colour vision depends on the vegetative nervous system; adrenaline applied to the conjunctivae increases the green and blue vision and decreases the red and orange one, pilocarpine acting *vice versa*. Rabkin found a practical method to measure the chromatic sensitivity of the eye and found it lowered in many diseases (glaucoma, optic neuritis, etc.). Bronstein, Zimkin and Lebedinsky by applying electrical irritation to the scalp produced phosphenes in the eye; experimenting on the wounded, they irritated the central neurones. They found that the irritation of the retinal neuron and the central nervous system neuron are going parallel one to the other.

As was said before, it is impossible to review completely the rich material of both volumes, and many of the papers are not described, not because of their lower status, but simply one cannot do justice to all of them.

The papers are accompanied by sketches of many ingenious apparatus, tablets and charts.

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Corrigendum

"SURGEON LIEUTENANT K. C. WYBAR writes to say that due to a misunderstanding the two references to Traquair's paper mentioned in his paper on Branch Thrombosis of Middle Cerebral Artery, Vol. XXIX, p. 355, are not quite accurately worded.